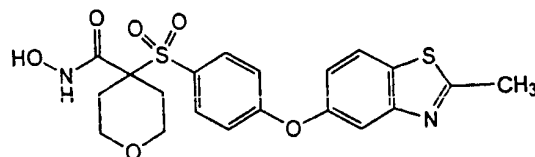


-501-



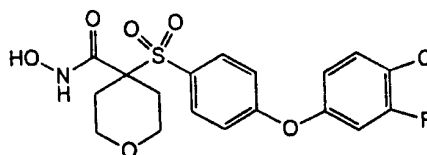
Step A: To a solution of the title compound of Example 55 (MW 387, 10g, 1.0 equivalents) in DMA (50mL) were added hydroxymethyl benzothiazole (8 g, 1.5 equivalents) followed by cesium carbonate (20 g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was cooled then filtered, the N,N-dimethylacetamide was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The desired solid separated out of solution as a gum. This gum was dissolved in ethyl acetate (100 mL) and was washed with water and dried over sodium sulfate. The solvent was removed in vacuo to give an oil that was dissolved in water/acetonitrile, made acidic with trifluoroacetic acid (pH=2), then purified on prep RPHPLC to give the 2-methyl-5-benzothiazolyloxy compound. The ¹H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The 2-methyl-5-benzothiazolyloxy compound of Step A was stirred in aqueous HCl (20mL)/acetonitrile(20mL) for 1 hour. The solvent was concentrated and the solid that separated was filtered to give 6.5 g of the title compound. The ¹H NMR, MS, and HPLC were consistent with the desired

-502-

compound. MS (CI) M+H calculated for $C_{20}H_{20}N_2O_6S_2$: 448, found 448.

5 Example 122: Preparation of 4-[[4-(4-chloro-3-fluorophenoxy)phenyl]sulfonyl]-
tetrahydro-N-hydroxy-2H-pyran-4-
10 carboxamide



10

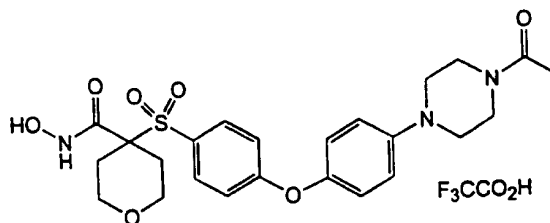
Step A: To a solution of the title compound of Example 55 (MW 387, 10 g, 1.0 equivalents) in N,N-dimethylacetamide (50 mL) were
15 added 4-chloro-3-fluorophenol (7 g, 1.4 equivalents) followed by cesium carbonate (20g, 2.0 equivalents). The reaction was heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had
finished. The reaction mixture was cooled then
20 filtered, the DMA was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The desired 4-chloro-3-fluorophenoxy compound (11 g) separated out of
solution and was filtered. The 1H NMR, MS, and HPLC
25 were consistent with the desired compound.

Step B: The 4-chloro-3-fluorophenoxy compound (3.4 g) of Step A was stirred in aqueous HCl (20 mL)/ acetonitrile(20 mL) for 1 hour. The solvent

-503-

was concentrated and the solid that separated was filtered to give 2.0 g of the title compound. The ^1H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for $\text{C}_{18}\text{H}_{17}\text{ClFNO}_6\text{S}$:
5 429, found 429.

Example 123: Preparation of 4-[[4-[4-(4-acetyl-1-piperazinyl)phenoxy]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-
10 carboxamide, trifluoroacetic acid salt

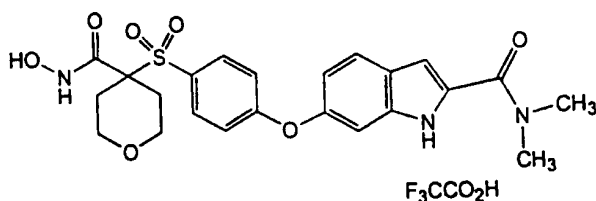


Step A: To a solution of the title
15 compound of Example 55 (MW 387, 5 g, 1.0 equivalents)
in DMA (50 mL) were added 1-acetyl-4-(4-hydroxy-
phenyl)piperazine (3 g, 2 equivalents) followed by
cesium carbonate (10g, 2.0 equivalents). The
reaction was heated at 90 degrees Celsius for 5
20 hours, until HPLC indicated the reaction had
finished. The reaction mixture was filtered, the DMA
was removed in vacuo. The residue was dissolved in
water/acetonitrile, made acidic with TFA (pH=2), then
purified on prep RPHPLC to give 3.1 g of the crude 4-
25 acetyl-1-piperazinylphenoxy compound as a brown
solid. The ^1H NMR, MS, and HPLC were consistent with
the desired compound.

-504-

Step B: The 4-acetyl-1-piperazinyloxy compound from reaction Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in
5 water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 2.0 g of tan foam as the trifluoroacetic acid salt of the title compound. The ¹H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for C₂₄H₂₉N₃O₇S
10 C₂HF₃O₂: 617, found 617.

Example 124: Preparation of N,N-dimethyl-5-[4-
[[tetrahydro-4-[(hydroxyamino)-
carbonyl]-2H-pyran-4-yl]sulfonyl]-
15 phenoxy]-1H-indole-2-carboxamide,
trifluoroacetic acid salt



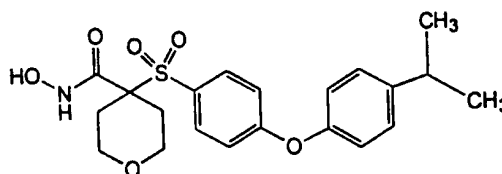
20 Step A: To a solution of the title compound of Example 55 (MW 387, 5g, 1.0 equivalents) in DMA (50 mL) were added the 5-hydroxy-2-indole dimethylcarboxylate (3 g, 2 equivalents) followed by Cs₂CO₃ (10 g, 2.0 equivalents). The reaction was
25 heated at 90 degrees Celsius for 5 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA was removed in vacuo.

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The residue was dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 2.1 g of the crude THP-protected pyran hydroxamate compound as a brown solid. The ¹H NMR, MS, and HPLC were consistent with the desired compound.

Step B: The THP-protected pyran hydroxamate compound from Step A was stirred in aqueous HCl (50 mL) for 1 hour. The solvent was removed and the residue was dried and dissolved in water/acetonitrile, made acidic with TFA (pH=2), then purified on prep RPHPLC to give 1.5 g of tan solid as the trifluoroacetic acid salt of the title compound. The ¹H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for C₂₃H₂₅N₃O₇S: 487, found 487.

Example 125: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Step A: To a solution of the title compound of Example 55 (MW 387, 5 g, 1.0 equivalents) in DMA (50 mL) was added the 4-isopropylphenol (3 g, 2 equivalents), followed by cesium carbonate (10 g, 2.0 equivalents). The reaction mixture was heated at

-506-

90 degrees Celsius for 8 hours, until HPLC indicated the reaction had finished. The reaction mixture was filtered, the DMA portion was discarded. The filter cake was placed in 10% aqueous HCl and stirred for 30 minutes to remove the cesium salts. The solid (3.5 g) isopropylphenoxyphenyl THP-protected hydroxamate separated and was filtered. The ¹H NMR, MS, and HPLC were consistent with the desired compound.

Step B: Into a stirred solution of aqueous HCl (20 mL) and acetonitrile (20 mL) was added the crude isopropyl-phenoxyphenyl THP-protected hydroxamate from Step A and the resulting mixture was stirred for 1-2 hours. The solvent was concentrated via a stream of nitrogen over the surface of the solution. The solid was filtered and dried to give 2.2 g of the title compound as a tan solid. The ¹H NMR, MS, and HPLC were consistent with the desired compound. MS (CI) M+H calculated for C₂₁H₂₅NO₆S: 419, found 419.

20

Example 126: Preparation of Resin II:

Step 1: Attachment of Compound
of Example 55, Part D, to Resin I

25 A 500 mL round-bottomed flask was charged with of resin I [Floyd et al., Tetrahedron Lett. 1996, 37, 8045-8048] (8.08 g, 9.7 mmol) and 1-methyl-2-pyrrolidinone (50 mL). A magnetic stirring bar was added, and the resin slurry slowly stirred. A separate solution of the compound of Part D, Example 30 55 (5.58 g, 19.4 mmol) in 1-methyl-2-pyrrolidinone (35

-507-

mL) was added to the slurry followed by addition of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (10.1 g, 19.4 mmol) in one portion. Once the hexafluorophosphate salt had dissolved, 4-methylmorpholine (4.26 mL, 39 mmol) was added dropwise. The reaction slurry was stirred at room temperature for 24 hours, then the resin was collected in a sintered-disc funnel and washed with N,N-dimethylformamide, methanol, methylene chloride and diethyl ether (3x30 mL each solvent). The resin was dried in vacuo to yield 10.99 g polymer-bound hydroxamate as a tan polymeric solid. Theoretical loading on polymer was 0.91 mmol/g. FTIR microscopy showed bands at 1693 and 3326 cm^{-1} indicative of the hydroxamate carbonyl and nitrogen-hydrogen stretches, respectively.

Step 2: Preparation of Resin III:

Reaction of Resin II With

Nucleophiles

Resin II (50 mg, 0.046 mmol) was weighed into an 8 mL glass vial, and a 0.5 M solution of a nucleophile in 1-methyl-2-pyrrolidinone (1 mL) was added to the vessel. In the case of phenol and thiophenol nucleophiles, cesium carbonate (148 mg, 0.46 mmol) was added, and in the case of substituted piperazine nucleophiles, potassium carbonate (64 mg, 0.46 mmol) was added. The vial was capped and heated to 70 to 155 degrees Celsius for 24-48 hours, then cooled to room temperature. The resin was drained and washed with 1-methyl-2-pyrrolidinone, 1-methyl-2-

-508-

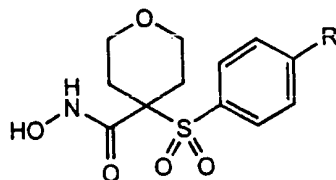
pyrrolidinone/water (1:1), water, 10% acetic acid/water, methanol, and methylene chloride (3x3 mL each solvent).

Step 3: Cleavage of Hydroxamic Acids
From The Polymer-Support

Resin III was treated with a trifluoroacetic acid/ water mixture (19:1, 1 mL) for 1 hour at room temperature. During that time, the resin became a deep red color. The resin was then drained and washed with trifluoroacetic acid/water (19:1) and methylene chloride (2x1 mL each solvent), collecting the combined filtrates in a tared vial. The volatiles were removed in vacuo, then a toluene/methylene chloride mixture (2 mL each) was added to the residue. The mixture was again concentrated in vacuo. The product was characterized by electrospray mass spectroscopy.

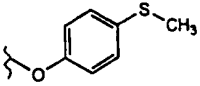
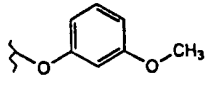
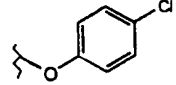
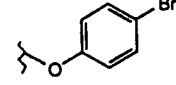
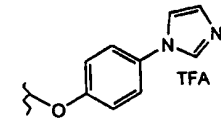
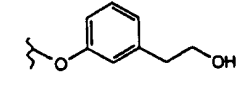
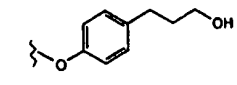
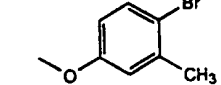
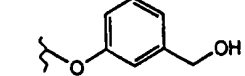
20 The following hydroxamic acids were synthesized from resin II using the conditions of Step 2 with the indicated nucleophile, followed by release from the polymer using Step 3 reaction conditions.

-509-

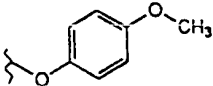
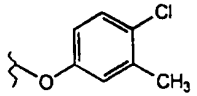
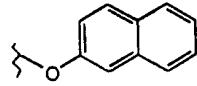
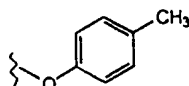
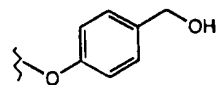
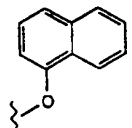
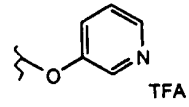
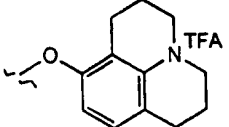
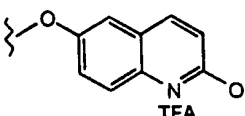


Example Number	R	Nucleophile	MS (ES)
			m/z
126-1		4'-hydroxy-2'- methylacetophenone	451 (M+NH ₄)
126-2		5,6,7,8-tetrahydro- 2-naphthol	455 (M+NH ₄)
126-3		3,4-dichlorophenol	462 (M+NH ₄)
126-4		4-hydroxyphenethyl alcohol	439 (M+NH ₄)
126-5		4-hydroxy diphenylmethane	485 (M+NH ₄)
126-6		4-phenylphenol	471 (M+NH ₄)

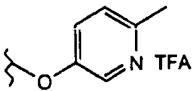
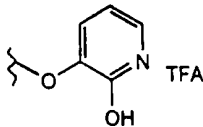
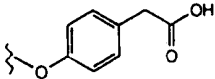
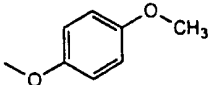
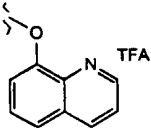
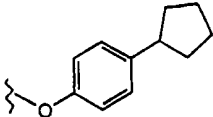
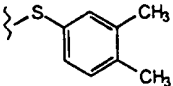
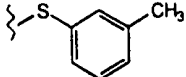
-510-

126-7		4-(methylthio)phenol	441 (M+NH ₄)
126-8		3-methoxyphenol	425 (M+NH ₄)
126-9		4-chlorophenol	429 (M+NH ₄)
126-10		4-bromophenol	590 (M+Cs)
126-11		4-(imidazol-1-yl)- phenol	444 (M+H)
126-12		3-hydroxyphenethyl alcohol	439 (M+NH ₄)
126-13		3-(4-hydroxy- phenyl)-1-phenol	453 (M+NH ₄)
126-14		4-bromo-3- methylphenol	487 (M+NH ₄)
126-15		3-hydroxybenzyl alcohol	425 (M+NH ₄)

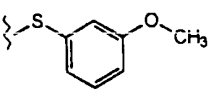
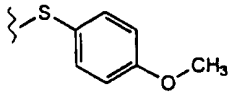
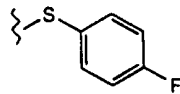
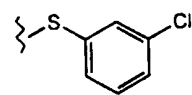
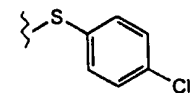
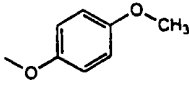
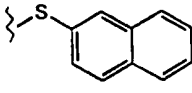
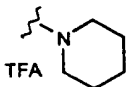
-511-

126-16		4-methoxyphenol	425 (M+NH ₄)
126-17		4-chloro-3-methylphenol	558 (M+Cs)
126-18		2-naphthol	560 (M+Cs)
126-19		p-cresol	409 (M+NH ₄)
126-20		4-hydroxybenzyl alcohol	408 (M+H)
126-21		1-naphthol	445 (M+NH ₄)
126-22		3-hydroxypyridine	379 (M+H)
126-23		8-hydroxyjulolidine	473 (M+H)
126-24		2,6-quinolinediol	445 (M+H)

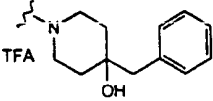
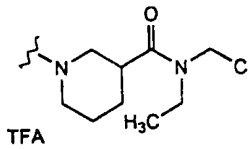
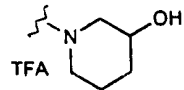
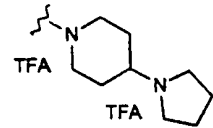
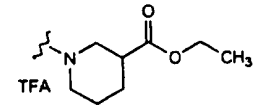
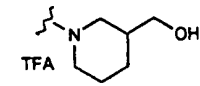
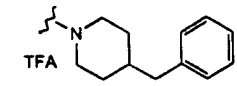
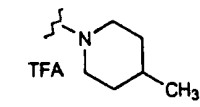
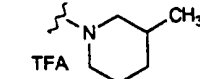
-512-

126-25		5-hydroxy-2-methylpyridine	393 (M+H)
126-26		2,3-dihydroxy-pyridine	412 (M+H)
126-27		4-hydroxyphenyl acetic acid	453 (M+NH ₄)
126-28		4-amino-m-cresol	407 (M+H)
126-29		8-quinolinol	429 (M+H)
126-30		4-cyclopentylphenol	463 (M+NH ₄)
126-31		3,4-dimethyl-thiophenol	439 (M+NH ₄)
126-32		m-thiocresol	425 (M+NH ₄)

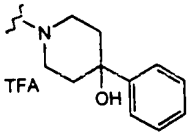
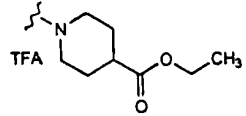
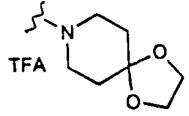
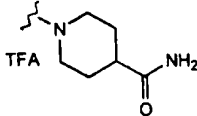
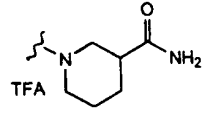
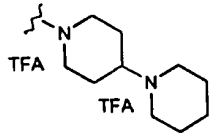
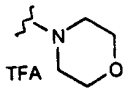
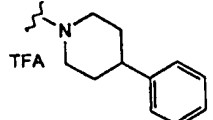
-513-

126-33		3-methoxythiophenol	441 (M+NH ₄)
126-34		4-methoxythiophenol	441 (M+NH ₄)
126-35		4-fluorothiophenol	429 (M+NH ₄)
126-36		3-chlorothiophenol	445 (M+NH ₄)
126-37		4-chlorothiophenol	445 (M+NH ₄)
126-38		4-aminothiophenol	426 (M+NH ₄)
126-39		2-naphthalenethiol	461 (M+NH ₄)
126-40		piperidine	

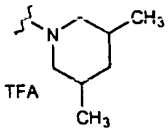
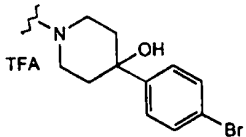
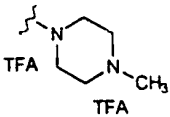
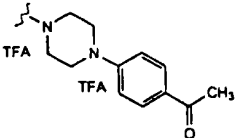
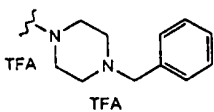
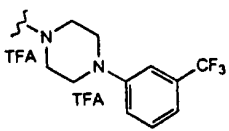
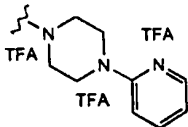
-514-

126-41		4-benzyl-4-hydroxypiperidine	475 (M+H)
126-42		nipecotamide	468 (M+H)
126-43		3-hydroxypiperidine	385 (M+H)
126-44		4-(1-pyrrolidinyl)-piperidine	438 (M+H)
126-45		ethyl nipecotate	441 (M+H)
126-46		3-piperidinyl-methanol	512 (M+TFA)
126-47		4-benzylpiperidine	459 (M+H)
126-48		4-methylpiperidine	383 (M+H)
126-49		3-methylpiperidine	383 (M+H)

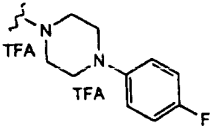
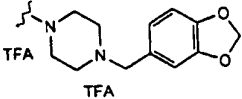
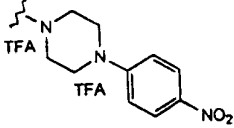
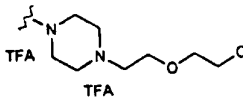
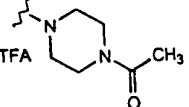
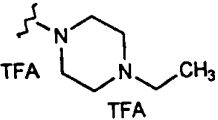
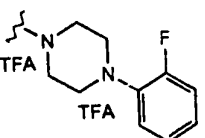
-515-

126-50		4-hydroxy-4-phenylpiperidine	461 (M+H)
126-51		ethyl isonipecotate	441 (M+H)
126-52		1,4-dioxaspiro(4,5)decane	427 (M+H)
126-53		isonipecotamide	412 (M+H)
126-54		nipecotamide	412 (M+H)
126-55		4-piperidino-piperidine	452 (M+H)
126-56		morpholine	388 (M+NH ₄)
126-57		4-phenylpiperidine	445 (M+H)

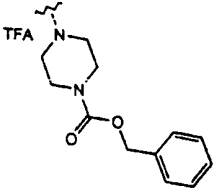
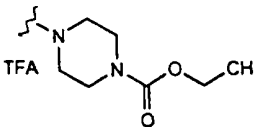
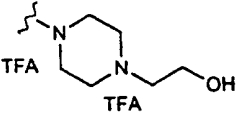
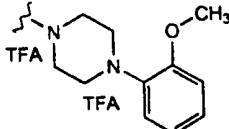
-516-

126-58		3,5-dimethyl- piperidine	414 (M+NH ₄)
126-59		4-(4-bromophenyl)-4- piperidinol	539 (M+H)
126-60		1-methylpiperazine	384 (M+H)
126-61		4-piperazino- acetophenone	488 (M+H)
126-62		1-benzylpiperazine	460 (M+H)
126-63		N-(α,α,α-trifluoro-m- tolyl)piperazine	514 (M+H)
126-64		1-(2-pyridyl)- piperazine	447 (M+H)

-517-

126-65		1-(4-fluorophenyl) - piperazine	464 (M+H)
126-66		1-piperonyl - piperazine	504 (M+H)
126-67		1-(4-nitrophenyl) - piperazine	491 (M+H)
126-68		1-hydroxyethyl - ethoxypiperazine	458 (M+H)
126-69		1-acetylpiperazine	412 (M+H)
126-70		1-ethylpiperazine	398 (M+H)
126-71		1-(2-fluorophenyl) - piperazine	464 (M+H)

-518-

126-72		benzyl-1-piperazine carboxylate	504 (M+H)
126		ethyl-N-piperazine carboxylate	442 (M+H)
127		N-(2-hydroxyethyl)- piperazine	414 (M+H)
128		1-(2-methoxy- phenyl)piperazine	476 (M+H)

Example XX: Large Scale Preparation of Resin IIIa

Resin II (5 g, 0.91 mmol) was weighed into an oven-dried three-necked round bottom flask fitted with a temperature probe, an overhead stirring paddle, and a nitrogen inlet. Anhydrous 1-methyl-2-pyrrolidinone (35 mL) was added to the flask followed by ethyl isonipecotate (7.0 mL, 45.5 mmol). The resin slurry was stirred slowly with the overhead stirrer, and the mixture was heated to 80 degrees Celsius with a heating mantle for 65 hours. The flask was thereafter cooled to room temperature.

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The resin was collected in a sintered-disk glass funnel and washed with N,N-dimethylformamide, methanol and methylene chloride (3X30 mL each solvent). The resin was dried in vacuo to provide 5 5.86 g of resin IIIa as off-white resin beads. The theoretical loading of the polymer was 0.81 mmol/g. TFA cleavage performed on 50 mg of resin IIIa as described in step 3 yielded 10.4 mg of off-white solid spectroscopically indistinguishable from the 10 reaction product using ethyl isonipecotate of Example 211.

Example YY: Large Scale Preparation of Resin IIIb:

Preparation of resin IIIb followed the 15 procedure described for preparation of resin IIIa, except ethyl nipecotate was substituted for ethyl isonipecotate. The yield after drying in vacuo was 5.77 g of resin IIIb as pale yellow resin beads. The theoretical loading of the polymer was 0.81 mmol/g. 20 TFA cleavage performed on 50 mg of resin IIIb as described in step 3 yielded 14.7 mg of off-white solid spectroscopically indistinguishable from the reaction product using ethyl nipecotate of Example 212.

25

Step 4: Hydrolysis of Polymer-Bound
Ester: Preparation of
Resin IVa

Resin IIIa (5.8 g, 4.5 mmol) was weighed 30 into a three-necked round bottomed flask fitted with an overhead stirring paddle. 1,4-Dioxane was added

-520-

to the flask, and the resin slurry was stirred for 15 minutes. Then, a 4 M solution of KOH (5 mL, 20 mmol) was added, and the mixture was stirred for 44 hours. The resin was thereafter collected in a sintered-disk
5 glass funnel and washed with dioxane/water (9:1), water, 10% acetic acid/water, methanol and methylene chloride (3X30 mL each solvent). The resin was dried in vacuo to yield 5.64 g of resin IVa as off-white polymer beads. FTIR microscopy showed bands at 1732
10 and 1704 cm^{-1} and a broad band from 2500-3500 cm^{-1} . The theoretical loading of the polymer-bound acid was 0.84 mmol/g.

Preparation of Resin IVb:

15 Using the procedure described in Step 4, resin IIIb (5.71 g, 4.5 mmol) was converted into 5.61 g of resin IVb. FTIR microscopy showed bands at 1731 and 1705 cm^{-1} and a broad band from 2500-3500 cm^{-1} . The theoretical loading of the polymer-bound acid was
20 0.84 mmol/g.

Step 5: Amide Bond Formation:

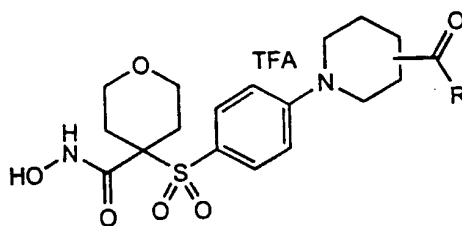
Preparation of Resin V

Into a fritted reaction vessel was weighed
25 either resin IVa or resin IVb (50 mg, 0.042 mmol), and the vessel was capped under nitrogen. A 0.5 M solution of hydroxybenzotriazole in 1-methyl-2-pyrrolidinone (0.3 mL, 0.15 mmol) was added followed by a 0.5 M solution of diisopropylcarbodiimide in 1-
30 methyl-2-pyrrolidinone (0.3 mL, 0.15 mmol). The resin was stirred using a tabletop stirring plate for

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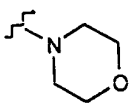
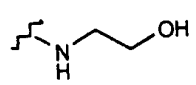
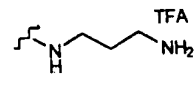
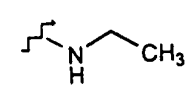
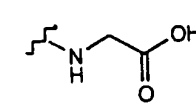
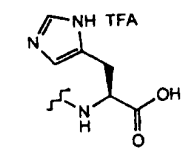
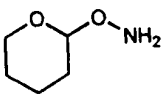
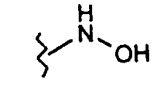
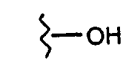
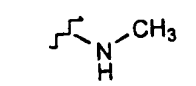
15 minutes, then a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) was added. The reaction mixture was stirred for 6 hours, then the resin was drained and washed with 1-methyl-2-pyrrolidinone (3X1mL). The reaction was repeated using the same amounts of reagents described above. The reaction mixture was stirred for 16 hours, then the resin was drained and washed with 1-methyl-2-pyrrolidinone, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized using the indicated polymer-bound acid and the indicated amine in Step 5 reaction conditions followed by release from the polymer using Step 3 reaction conditions.

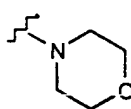
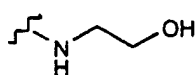
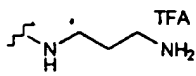
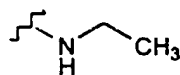
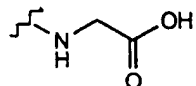
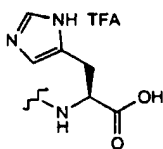
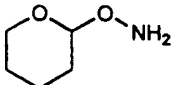
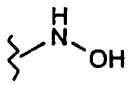
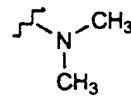
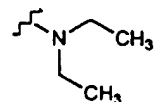


Example Number	Resin	Amine	R	Position	MS (ES)
					m/z
129	IVa	-----	---OH	4	
130	IVa	methylamine	---NH---CH_3	4	

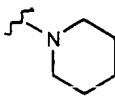
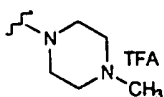
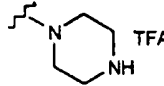
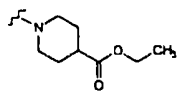
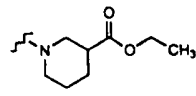
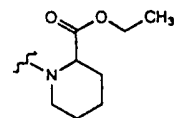
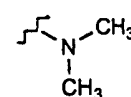
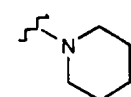
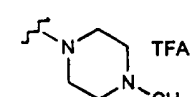
-522-

131	IVa	morpholine		4	482 (M+H)
132	IVa	ethanolamine		4	456 (M+H)
133	IVa	1,3-diamino- propane		4	469 (M+H)
134	IVa	ethylamine		4	440 (M+H)
135	IVa	glycine t- butyl ester HCl		4	470 (M+H)
136	IVa	L-histidine methyl ester HCl		4	564 (M+H)
137	IVa			4	428 (M+H)
138	IVb	-----		3	
139	IVb	methylamine		3	426 (M+H)
140	IVb	morpholine		3	482 (M+H)

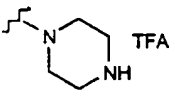
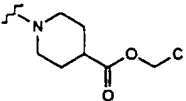
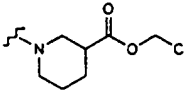
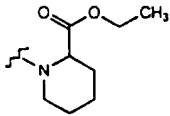
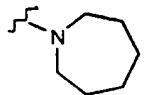
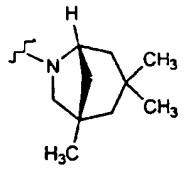
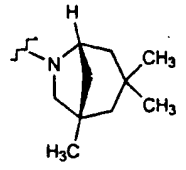
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141	IVb	ethanolamine		3	456 (M+H)
142	IVb	1,3-diamino- propane		3	469 (M+H)
143	IVb	ethylamine		3	440 (M+H)
144	IVb	glycine t- butyl ester HCl		3	470 (M+H)
145	IVb	L-histidine methyl ester HCl		3	564 (M+H)
146	IVb			3	428 (M+H)
147	IVa	dimethylamine		4	440 (M+H)
148	IVa	diethylamine		4	468 (M+H)

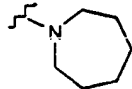
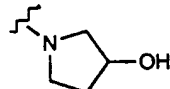
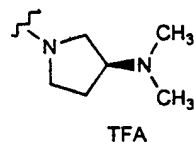
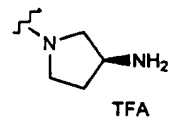
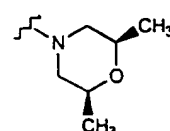
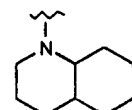
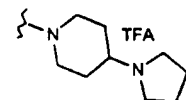
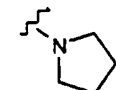
-524-

149	IVa	piperidine		4	480 (M+H)
150	IVa	1-methyl- piperazine		4	495 (M+H)
151	IVa	N-Boc- piperazine		4	481 (M+H)
152	IVa	ethyl isonipecotate		4	552 (M+H)
153	IVa	ethyl nipecotate		4	552 (M+H)
154	IVa	ethyl pipecolate		4	552 (M+H)
155	IVb	dimethylamine		3	440 (M+H)
156	IVb	piperidine		3	480 (M+H)
157	IVb	1-methyl- piperazine		3	495 (M+H)
158	IVb	N-Boc-		3	481

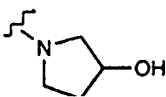
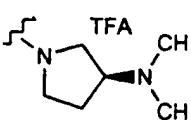
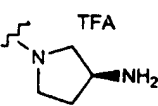
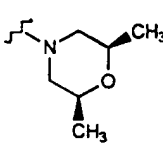
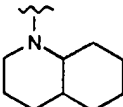
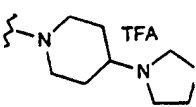

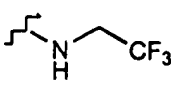
-525-

		piperazine			(M+H)
159	IVb	ethyl isonipecotate		3	552 (M+H)
160	IVb	ethyl nipecotate		3	552 (M+H)
161	IVb	ethyl pipecolate		3	552 (M+H)
162	IVb	hexamethylene- imine		3	494 (M+H)
163	IVb	1,3,3- trimethyl-6- azabicyclo [3.2.1]-octane		3	548 (M+H)
164	IVa	1,3,3- trimethyl-6- azabicyclo [3.2.1]-octane		4	548 (M+H)

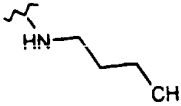
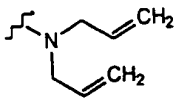
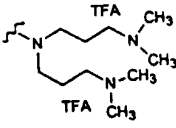
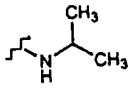
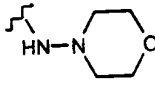
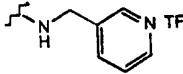
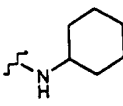
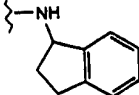
-526-

165	IVa	hexamethylene- imine		4	494 (M+H)
166	IVb	3-pyrrolidinol		3	482 (M+H)
167	IVb	(3S) - (-) - 3- (dimethyl amino) - pyrrolidine		3	509 (M+H)
168	IVb	(3S) - (-) - 3- (t-butoxy- carbonylamino) -pyrrolidine		3	481 (M+H)
169	IVb	cis-2,6- dimethyl- morpholine		3	510 (M+H)
170	IVb	decahydro- quinoline		3	534 (M+H)
171	IVb	4-(1- pyrrolidinyl) - piperidine		3	549 (M+H)
172	IVb	pyrrolidine		3	466 (M+H)

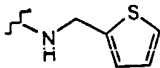
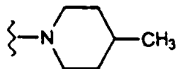
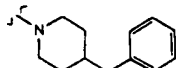
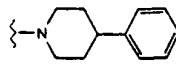
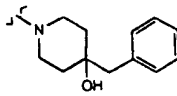
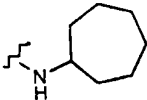
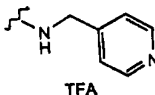
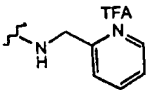
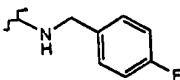
-527-

173	IVa	3-pyrrolidinol		4	482 (M+H)
174	IVa	(3S)-(-)-3-(dimethylamino)-pyrrolidine		4	509 (M+H)
175	IVa	(3S)-(-)-3-(t-butoxycarbonylamino)-pyrrolidine		4	481 (M+H)
176	IVa	cis-2,6-dimethyl-morpholine		4	510 (M+H)
177	IVa	decahydroquinoline		4	534 (M+H)
178	IVa	4-(1-pyrrolidinyl)-piperidine		4	549 (M+H)
179	IVa	pyrrolidine		4	466 (M+H)
180	IVa	2,2,2-trifluoroethylamine		4	494 (M+H)

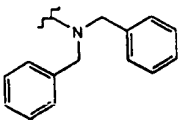
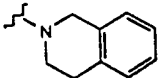
-528-

181	IVa	butylamine		4	468 (M+H)
182	IVa	diallylamine		4	492 (M+H)
183	IVa	3,3'- iminobis(N,N- dimethylpropyl -amine)		4	582 (M+H)
184	IVa	iso- propylamine		4	454 (M+H)
185	IVa	4-amino- morpholine		4	497 (M+H)
186	IVa	3- (aminomethyl)- pyridine		4	503 (M+H)
187	IVa	cyclohexyl- amine		4	494 (M+H)
188	IVa	1-aminoindane		4	528 (M+H)

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189	IVa	2-thiophene- methylamine		4	508 (M+H)
190	IVa	4-methyl- piperidine		4	494 (M+H)
191	IVa	4-benzyl- piperidine		4	570 (M+H)
192	IVa	4-phenyl- piperidine		4	556 (M+H)
193	IVa	4-benzyl-4- hydroxy- piperidine		4	586 (M+H)
194	IVa	cycloheptyl- amine		4	508 (M+H)
195	IVa	4-aminomethyl- pyridine		4	503 (M+H)
196	IVa	2-amino- methyl- pyridine		4	503 (M+H)
197	IVa	4-fluoro- benzylamine		4	520 (M+H)

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198	IVa	dibenzylamine		4	592 (M+H)
199	IVa	1,2,3,4-tetrahydro-isoquinoline		4	528 (M+H)

Large Scale Preparation of Resin IIIc

Resin II (3.01 g, 2.74 mmol) was weighed
5 into an oven-dried three-necked round bottomed flask
fitted with an overhead stirring paddle, a
temperature probe and an nitrogen inlet. 1-Methyl-2-
pyrrolidinone (25 mL) was added followed by
piperazine (2.36 g, 27.4 mmol) and cesium carbonate
10 (8.93 g, 27.4 mmol). Additional 1-methyl-2-
pyrrolidinone (10 mL) was added, and the reaction
mixture was heated to 100 degrees Celsius and stirred
18 hours. The flask was cooled to room temperature,
and the resin was collected in a sintered-disc funnel
15 and washed with N,N-diethylformamide/water (1:1),
water, 10% acetic acid/water, methanol, and methylene
chloride (3X30 mL each solvent). The yield after
drying in vacuo was 3.14 g of resin IIIb as pale
yellow resin beads. The theoretical loading of the
20 polymer was 0.86 mmol/g. TFA cleavage performed on
50 mg of resin IIIb as described in Step 3 yielded 21
mg of off-white solid spectroscopically
indistinguishable from the compound of Example 209.

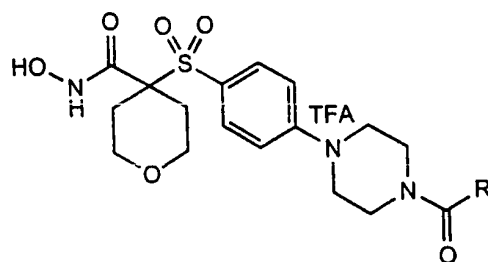
-531-

Step 6: Amide Bond Formation with
resin IIIc: Preparation of
Resin VI

5 Into a fritted reaction vessel was placed
the carboxylic acid (0.215 mmol) and 1-
hydroxybenzotriazole (44 mg, 0.326 mmol). The vessel
was capped under nitrogen, and 1-methyl-2-
pyrrolidinone was added followed by
10 diisopropylcarbodiimide (0.034 mL, 0.215 mmol). The
solution was agitated on a tabletop shaker for 15
minutes, then resin IIIc (50 mg, 0.043 mmol) was
added in one portion. The reaction mixture was
shaken for 16 hours, then the resin was drained and
15 washed with 1-methyl-2-pyrrolidinone, methanol and
methylene chloride (3X1 mL each solvent). In the
case of N-9-fluorenyl-methoxycarbonyl-protected amino
acids, the resin was further treated with a
piperidine/N,N-dimethylformamide solution (1:4, 1 mL)
20 for 30 minutes. The resin was drained and washed with
N,N-dimethylformamide, methanol and methylene
chloride (3X1 mL each solvent).

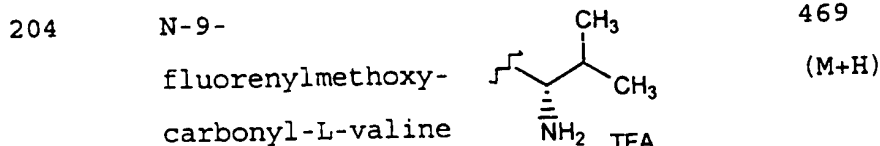
The following hydroxamic acids were
25 synthesized from resin IIIc using Step 6 with the
indicated carboxylic acid, followed by release from
the polymer using Step 3 reaction conditions.

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Example Number	Carboxylic Acid	R	MS (ES) m/z
200	cyclo-hexanecarboxylic acid		502 (M+Na)
201	1,2,3,4-tetrahydronaphthylene-2-carboxylic acid		545 (M+NH ₄)
202	cycloheptane-carboxylic acid		511 (M+NH ₄)
203	N-9-fluorenylmethoxy-carbonyl-L-proline	 TFA	467 (M+H)

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Step 7: Preparation of Resin VII

5 Resin IIIc (1.0g, 0.86 mmol) was weighed into an oven-dried 100 mL round-bottomed flask and a magnetic stirring bar and septum with a nitrogen needle were added. Methylene chloride (10 mL) was added, and the resin slurry was slowly stirred. p-
10 Nitrophenylchloro-formate (0.867 g, 4.3 mmol) was added in one portion, followed by dropwise addition of diisopropylethylamine (0.75 mL, 4.3 mmol). A slight warming was noted with the addition. The reaction was stirred at room temperature for 18
15 hours, then the resin was collected in a sintered-disc glass funnel and washed with methylene chloride, methanol and methylene chloride (3X10 mL each solvent).

 The polymer-bound product was dried in
20 vacuo yielding 1.25 g of resin VII as brown resin beads. FTIR microscopy showed bands at 1798, 1733, 1696 and 1210 cm^{-1} . Theoretical loading of the polymer was 0.75 mmol/g.

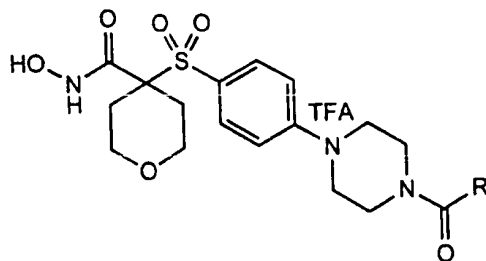
-534-

Step 8: Reaction of Resin VII with
Amines Preparation of
Resin VIII

An 8 mL vial was charged with resin VII (50
5 mg, 0.038 mmol) and a small magnetic stirring bar,
and a 0.5 M solution of the amine in 1-methyl-2-
pyrrolidinone (1 mL) was added. The vial was capped
and heated to 50 degrees Celsius. The resin slurry
was gently stirred for 15 hours, then the vial was
10 cooled to room temperature. The resin was collected
in a fritted reaction vessel and washed with 1-
methyl-2-pyrrolidinone, methanol and methylene
chloride (3X10 mL each solvent).

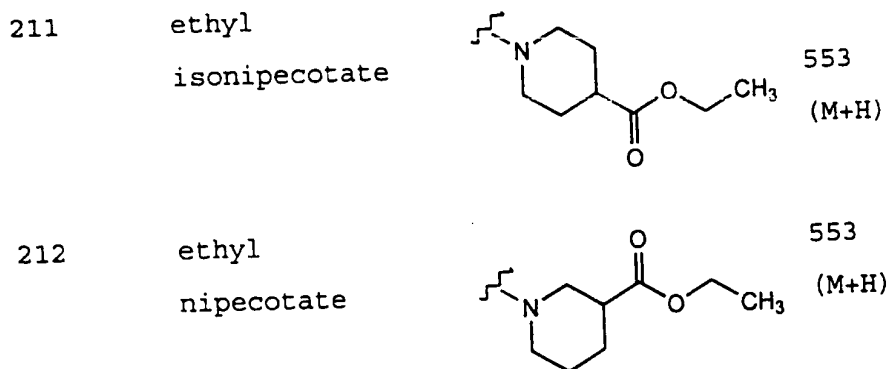
The following hydroxamic acids were
15 synthesized from resin VII using Step 8 reaction
conditions with the indicated amine, followed by
release from the polymer using Step 3 reaction
conditions.

-535-

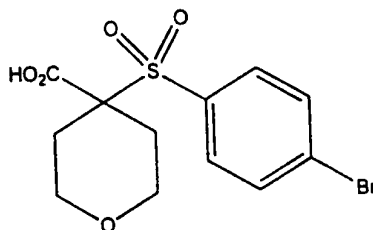


Example Number	Carboxylic Acid	R	MS (ES) m/z
205	-----		535 (M+H)
206	piperidine		481 (M+H)
207	morpholine		501 (M+Na)
208	dimethylamine		441 (M+H)
209	piperazine		482 (M+H)
210	1-methyl-piperazine		496 (M+H)

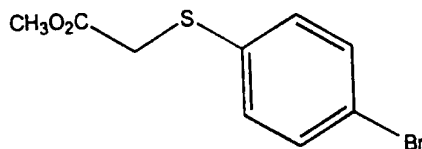
-536-



Example xxx: Preparation of 4-[(4-bromophenyl)-
sulfonyl]tetrahydro-2H-
pyran-4-carboxylic acid



Part A: Preparation of



A 60% sodium hydride oil dispersion (4.0 g,
0.1 mole) was weighed into an oven-dried 3-necked 500
mL round-bottomed flask in a nitrogen glove bag, and

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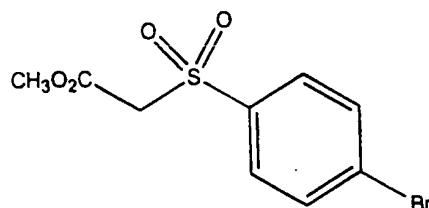
the flask was fitted with an nitrogen inlet, a temperature probe, an overhead stirring paddle and rubber septa. Anhydrous tetrahydrofuran (200 mL) was added to the flask, which was then cooled in an ice bath. 4-Bromothiophenol (18.91 g, 0.1 mole) was added dropwise, maintaining a temperature less than 7 degrees Celsius. Vigorous gas evolution was noted throughout addition. After complete addition, the mixture was stirred for 10 minutes with cooling.

Then, methyl bromoacetate (9.5 mL, 0.1 mole) was added dropwise, maintaining a temperature less than 7 degrees Celsius. The reaction was stirred for 10 minutes with cooling, then the ice bath was removed and the mixture stirred an additional 30 minutes.

The reaction was quenched by the addition of 5 mL water, then solvent was removed on rotary evaporator. The residual oil was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with 5% hydrogen choride/water (1x200 mL), saturated sodium bicarbonate (1x200 mL) and brine (1x200 mL). The organic phase was dried over magnesium sulfate and concentrated to give 24.53 g of the product as a yellow oil (94%). ¹H NMR was consistent with the desired structure. The mass spectrum showed an m/z 260 (M+H).

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Part B: Preparation of



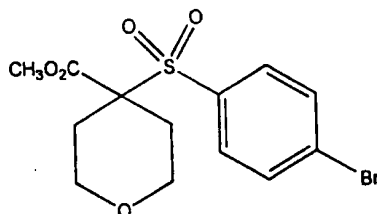
5 The compound of part A, above, (24.5 g, 0.094 mole) was weighed into a 1.0 L round-bottomed flask fitted with an overhead stirring paddle and temperature probe, then 550 mL of methanol were added, followed by 55 mL of water, causing the
10 solution to become slightly turbid. The flask was immersed in an ice bath, and once the temperature fell below 5 degrees Celsius, Oxone® (144.5 g, 0.235 mole) was added portionwise over 5 minutes. A slight increase in temperature to 8 degrees Celsius was
15 noted. The reaction was stirred with cooling for 10 minutes, then the ice bath was removed. After 4 hours, reversed-phase high pressure liquid chromatography showed a single component at 13.6 minutes. The reaction mixture was filtered, and the
20 solid washed exhaustively with methanol. The combined filtrates were concentrated on a rotary evaporator, and the residual material partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (3x200 mL),
25 saturated sodium bicarbonate (1x200 mL) and brine (1x200 mL), then the organic phase was dried over magnesium sulfate and concentrated to give 25 g of

-539-

the product as a tan solid. Trituration with hexane provided 24.3 g of pure sulfone as an off-white solid (88%). ¹H NMR was consistent with the desired structure. The mass spectrum showed an *m/z* 293 (M+H).

10

Part C: Preparation of



A 60% sodium hydride oil dispersion (5.76 g, 0.144 mole) was weighed into an oven-dried 3-necked 1.0 L round-bottomed flask in a nitrogen glove bag, and then the flask was fitted with a nitrogen inlet, a temperature probe, an overhead stirring paddle and rubber septa. Anhydrous N,N-dimethylformamide (250 mL) was added to the flask, mechanical stirring was initiated, and the mixture heated to 50 degrees Celsius. A solution of the compound of part B, above, (17.59 g, 0.06 mole) and dibromodiethyl ether (14.5 g, 0.06 mole) in 40 mL of N,N-dimethylformamide was added dropwise to the sodium hydride slurry, maintaining a temperature between 50-55 degrees Celsius and a steady evolution of hydrogen. After complete addition, the

-540-

temperature of the reaction mixture was increased to 65 degrees Celsius, and the mixture was stirred for 2 hours. The flask was then cooled to room temperature, and the flask was immersed in an ice bath. When the temperature fell below 20 degrees Celsius, 0.5 L ice water was added.

The mixture was transferred to a 4.0 L separatory funnel, an additional 1.0 L of water was added, and the mixture was extracted with ethyl acetate (3x200 mL). The combined organic layers were washed with 5% hydrogen chloride/water (1x200 mL), saturated sodium carbonate (1x200 mL), and brine (1x200 mL), dried over magnesium sulfate, and concentrated in vacuo to give 18.2 g of crude product as a yellow semi-solid. Recrystallization from ethyl acetate/hexane gave 6.53 g of pure product as tan crystals (30%). ¹H NMR was consistent with the desired structure. The mass spectrum showed an *m/z* 363 (M+H).

Part D: Preparation of the Title compound

A solution of the compound of part C, above, (4.57 g, 12.6 mmol) in 50 mL of dry tetrahydrofuran in an oven-dried 100 mL round-bottomed flask was stirred at room temperature under nitrogen, and 4.84 g of potassium trimethylsilanolate (37.7 mmol) were added in one portion. The mixture was stirred for two hours, then 10 mL of water were added dropwise. The volatiles were removed in vacuo, and the residue partitioned between 100 mL ethyl ether and 100 mL water. The aqueous layer was acidified to a pH value of less than 2 using

-541-

concentrated hydrogen chloride, causing a white precipitate. This mixture was extracted with ethyl acetate (3x75 mL), and the combined ethyl acetate layers were dried over magnesium sulfate and concentrated in vacuo to give 4.15 g of pure product as a white solid (94%). ¹H NMR (CDCl₃/CD₃OD) 2.10 (m, 4H), 3.28 (m, 2H), 3.90 (m, 2H), 7.60 (m, 4 H). The mass spectrum showed an m/z 349 (M+H).

10

Step 9: Attachment to Resin I:

Preparation of Resin IX

Following the procedure outlined in Step 1 before, 3.13 g of the title compound of the above preparation was reacted with 3.73 g of resin I to give 5.19 g of polymer-bound hydroxamate as a tan polymeric solid. Theoretical loading on polymer was 0.86 mmol/g. FTIR microscopy showed bands at 1693 and 3332 cm⁻¹ indicative of the hydroxamate carbonyl and nitrogen-hydrogen stretches, respectively.

20

Step 10: Palladium Catalyzed Reaction
of Resin IX with Boronic
Acids: Preparation of
Resin VII

25

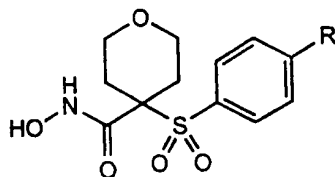
Into an 8 mL glass solid phase reaction vessel was weighed resin IX (50 mg, 0.043 mmol). The resin was washed with dry dimethoxyethane (2x3 mL). A 0.017 M solution of the palladium tetrakis(triphenyl phosphine) (0.6 mL, 0.01 mmol) was added to the vessel followed by a 0.6 M solution of the boronic acid in 1:1 dimethoxyethane /ethanol (0.6 mL, 0.36 mmol) and

30

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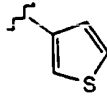
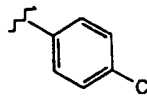
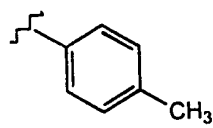
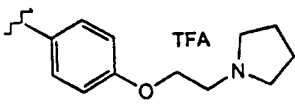
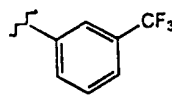
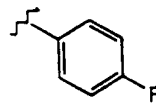
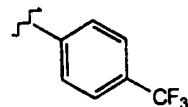
a 2M solution of potassium hydroxide in water (0.4 mL, 0.8 mmol). The vessel was maintained under a positive pressure of argon and heated at 90 degrees Celsius 16 hours. The vessel was cooled to room temperature, then the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1-methyl-2-pyrrolidinone/water (1:1), water, acetic acid/water (1:9), methanol, and methylene chloride (3x3 mL each solvent).

The following hydroxamic acids were synthesized from resin IX using Step 10 reaction conditions with the indicated boronic acid, followed by cleavage from the polymer using Step 3 reaction conditions.

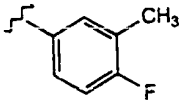
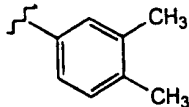
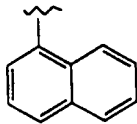
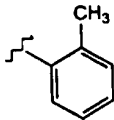
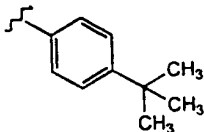
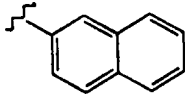
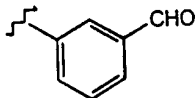
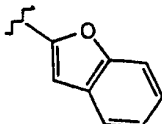


Example Number	Boronic Acid	R	MS
			(ES) m/z
213	phenylboronic acid		362 (M+H)
214	3-nitrophenyl-boronic acid		424 (M+NH ₄)

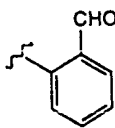
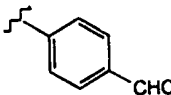
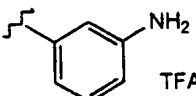
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215	thiophene-3- boronic acid		368 (M+H)
216	4-chlorobenzene boronic acid		413 (M+NH ₄)
217	4-methyl- benzeneboronic acid		414 (M+K)
218	4-(2- pyrrolidinyl- ethoxy)- benzeneboronic acid		476 (M+NH ₄)
219	3-(tri- fluoromethyl)- benzeneboronic acid		430 (M+H)
220	4-fluoro- benzeneboronic acid		418 (M+K)
221	4-(tri- fluoromethyl)- benzeneboronic acid		447 (M+NH ₄)

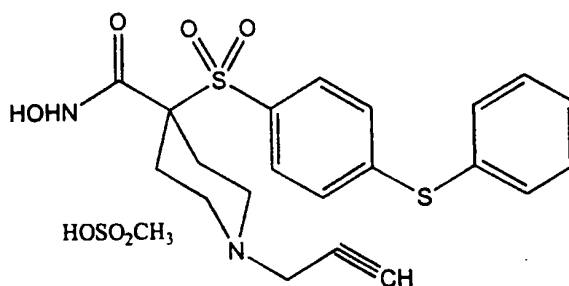
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222	4-fluoro-3-methylbenzeneboronic acid		411 (M+NH ₄)
223	3,4-dimethylbenzeneboronic acid		407 (M+NH ₄)
224	1-naphthyleneboronic acid		412 (M+H)
225	2-methylbenzeneboronic acid		376 (M+H)
226	4-t-butylbenzeneboronic acid		418 (M+H)
227	2-naphthyleneboronic acid		412 (M+H)
228	3-formylbenzeneboronic acid		390 (M+H)
229	benzofuran-2-boronic acid		419 (M+NH ₄)

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230	2-formyl- benzeneboronic acid		390 (M+H)
231	4-formyl- benzeneboronic acid		390 (M+H)
232	3-amino- benzeneboronic acid		377 (M+H)

Example 233: Preparation of Monomethanesulfonate salts: N-hydroxy-4-[[4-(phenylthio)phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidine-carboxamide,
monomethanesulfonate



First Preparation

Part A: A solution of the compound of Example 9, Part J (2.1 g, 4.5 mmol) in warm H₂O (200 mL) was admixed with NaHCO₃ at ambient temperature.
 After stirring for 20 minutes, the resulting white

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solid was isolated by filtration, washed with water and dried at 37 degree Celsius in a vacuum oven to afford the free base of the title compound as a white solid (1.7 g, 86%); Anal. calcd for $C_{21}H_{22}N_2O_4S_2 \cdot 0.3H_2O$:
5 C, 57.86; H, 5.23; N, 6.43; S, 14.71. Found: C, 57.84; H, 4.96; N, 6.39; S, 14.89.

Part B: Methanesulfonic acid (0.28 mL, 4.1 mmol) was added to a solution of the free base of part A (1.6 g, 3.7 mmol) in methanol (10 mL) at
10 ambient temperature. After 3 hours, the resulting solid was isolated by filtration, washed with methanol, and dried at ambient temperature in a vacuum oven to afford the monomethanesulfonate titled
15 compound as a white solid (1.6 g, 81%): Anal. calcd for $C_{21}H_{22}N_2O_4S_2 \cdot CH_4O_3$: C, 48.51; H, 5.18; N, 5.14; S, 17.66. Found: C, 48.88; H, 5.15; N, 5.23; S, 17.81.

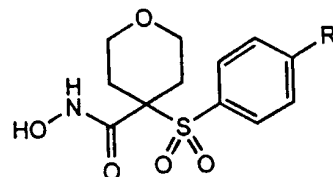
Second Preparation

Methanesulfonic acid (0.91 mL, 14 mmol) was
20 added to a solution of the protected hydroxamate of Example 9, Part I (6.0 g, 12 mmol) in methanol (37 mL) under a nitrogen atmosphere. After 1 hour, the precipitate was isolated by filtration, washed with methanol, and dried at 40 degrees Celsius in a vacuum
25 oven for 1 day to afford the monomethanesulfonate title compound as a white solid (5.5 g, 89%) identical to the material from Example 233, First Preparation.

Methanesulfonate salts of the other cyclic
30 amine compounds disclosed herein can be similarly prepared using the methods of the above two preparations.

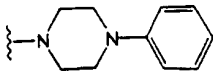
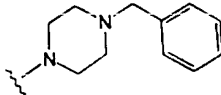
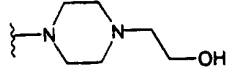
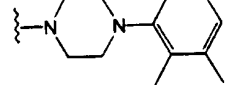
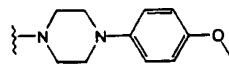
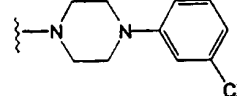
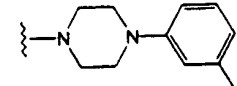
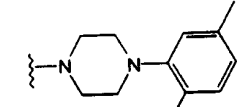
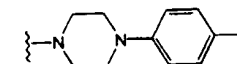
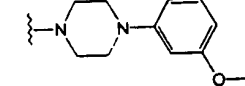
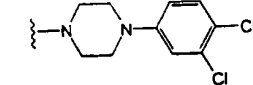
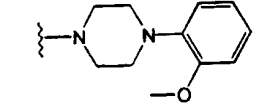
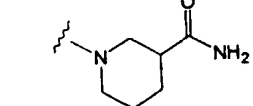
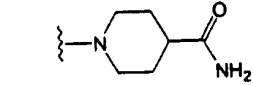
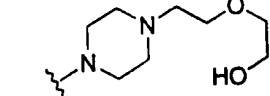
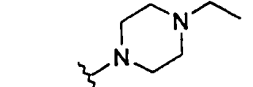
Example 234-280:

The compounds of Example 234-280 were prepared as described for the compounds of Example 5 129-199.



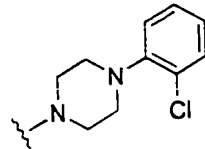
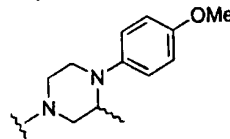
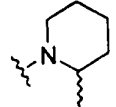
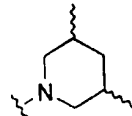
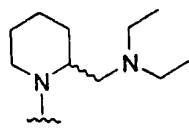
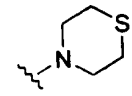
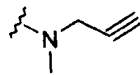
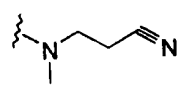
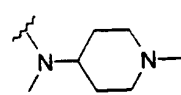
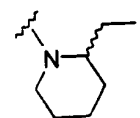
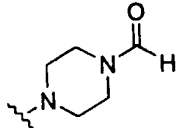
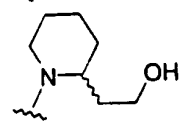
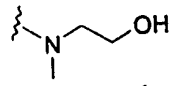
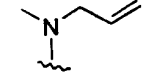
Example Number	Resin	Amine	R	Position	MS (ES) m/z
234	IVb	N-methyl homopiperazine		4	509 (M+H)
235	IVb	6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl		4	588 (M+H)
236	IVb	tetrahydro-pyridine		4	478 (M+H)
237	IVb	R-3-hydroxy-piperidine HCl		4	496 (M+H)
238	IVb	phenyl-piperazine		4	557 (M+H)
239	IVb	benzyl-piperazine		4	571 (M+H)
240	IVa	methyl homopiperazine		3	509 (M+H)
241	IVa	6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl		3	588 (M+H)
242	IVa	tetrahydro-pyridine		3	478 (M+H)
243	IVa	R-3-hydroxy-piperidine HCl		3	496 (M+H)

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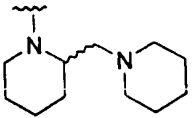
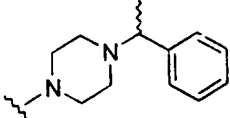
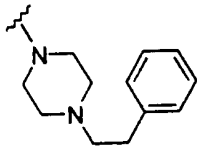
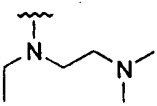
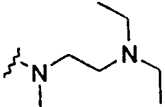
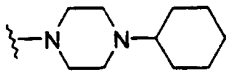
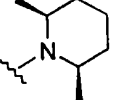
244	IVa	phenyl-piperazine		3	557 (M+H)
245	IVa	benzyl-piperazine		3	571 (M+H)
246	IVb	hydroxyethyl-piperazine		4	525 (M+H)
247	IVb	1-(2,3-xylyl)-piperazine HCl		4	585 (M+H)
247	IVb	1-(4-methoxyphenyl)-piperazine 2HCl		4	587 (M+H)
249	IVb	1-(3-chlorophenyl)-piperazine HCl		4	591 (M+H)
250	IVb	1-(m-tolyl)-piperazine 2HCl		4	571 (M+H)
251	IVb	1-(2,5-dimethylphenyl)piperazine		4	585 (M+H)
252	IVb	1-(p-toyl)-piperazine 2HCl		4	571 (M+H)
253	IVb	1-(3-methoxyphenyl)-piperazine 2HCl		4	587 (M+H)
254	IVb	1-(3,4-dichlorophenyl)piperazine		4	625 (M+H)
255	IVb	1-(2-methoxy)-piperazine HCl		4	587 (M+H)
256	IVb	nipecotamide		4	523 (M+H)
257	IVb	isonipecotamide		4	523 (M+H)
258	IVb	1-(2-(2-hydroxyethoxyethyl)-piperazine		4	569 (M+H)
259	IVb	1-ethyl-piperazine		4	509 (M+H)

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260	IVb	1-(2-chlorophenyl)-piperazine HCl		4	591 (M+H)
261	IVb	1-(4-methoxyphenyl)-2-methyl-piperazine		4	601 (M+H)
262	IVb	2-methyl-piperidine		4	494 (M+H)
263	IVb	3,5-dimethyl-piperidine		4	508 (M+H)
264	IVb	N-(2-piperidyl-methyl)-diethylamine		4	565 (M+H)
265	IVb	thiomorpholine HCl		4	498 (M+H)
266	IVb	N-methyl-propargylamine		4	464 (M+H)
267	IVb	N-methyl-β-alaninenitrile		4	479 (M+H)
268	IVb	1-methyl-4-(methyl-amino)piperidine		4	523 (M+H)
269	IVb	2-ethyl-piperidine		4	508 (M+H)
270	IVb	1-piperazine-carboxaldehyde		4	509 (M+H)
271	IVb	2-piperidin-ethanol		4	524 (M+H)
272	IVb	2-(methylamino)-ethanol		4	470 (M+H)
273	IVb	N-methylallyl-amine		4	466 (M+H)

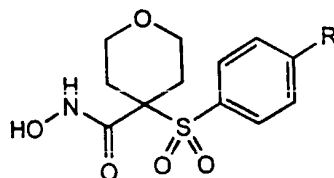
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274	IVb	2-(piperidino-methyl)-piperidine		4	577 (M+H)
275	IVb	1-(1-phenyl-ethyl)-piperazine		4	585 (M+H)
276	IVb	1-(2-phenyl-ethyl)-piperazine		4	585 (M+H)
277	IVb	N,N-dimethyl-N'-ethylene-diamine		4	511 (M+H)
278	IVb	N,N-diethyl-N-methylene-ethylenediamine		4	525 (M+H)
279	IVb	1-cyclohexyl-piperazine		4	563 (M+H)
280	IVb	2,6-dimethyl-piperidine		4	508 (M+H)

Example 281-288:

The following hydroxamic acids were
 5 synthesized from Resin IX using Step 10 with the
 indicated boronic acid, followed by cleavage from the
 polymer using Step 3, as discussed previously for
 Example 213-232:

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Example Number	Boronic acid	R	MS (ES) m/z
281	4-methoxybenzeneboronic acid		392 (M+H)
282	3-methoxybenzeneboronic acid		392 (M+H)
283	4-methylthiobenzeneboronic acid		408 (M+H)
284	4-MeNHSO ₂ -benzeneboronic acid		455 (M+H)
285	4-carboxybenzeneboronic acid		406 (M+H)
286	2-trifluoromethylbenzeneboronic acid		430 (M+H)
287	3,5-bis-(trifluoromethyl)-benzeneboronic acid		498 (M+H)
288	2,3,4-trifluorobenzeneboronic acid		416 (M+H)

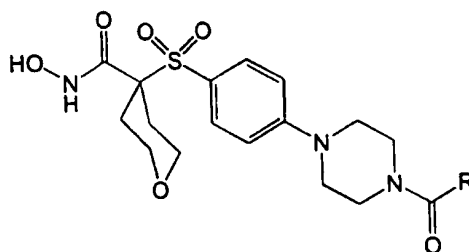
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Example 289-294:

Step 11: Preparation of Resin XI.

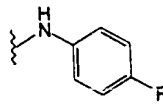
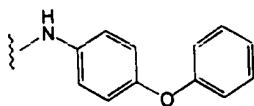
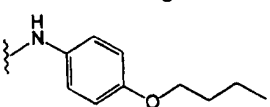
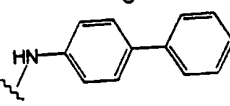
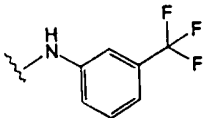
Into a fritted reaction vessel was placed Resin IIIc (50 mg, 0.043 mmol). A 0.43 M solution of the isocyanate in 1-methyl-2-pyrrolidinone (1 mL, 0.43 mmol) was added followed by diisopropylethylamine (75 uL, 0.43 mmol). The vessel was capped under nitrogen, agitated on a tabletop shaker, and heated to 50 degrees Celsius for 48 hours. Then, the vessel was cooled to room temperature, and the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from Resin IIIc using Step 11 with the indicated isocyanate, followed by release from the polymer using the reaction conditions in Step 3.



Example Number	Isocyanate	R	MS (FAB) m/z
289	phenyl isocyanate		489.1 (M+H)

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290	4-fluorophenyl isocyanate		507.2 (M+H)
291	4-phenoxyphenyl isocyanate		581.3 (M+H)
292	4-butoxyphenyl isocyanate		561.4 (M+H)
293	4-phenylphenyl- isocyanate		565.2 (M+H)
294	α,α,α -trifluoro m-tolyl isocyanate		557.2 (M+H)

Example 295-300:

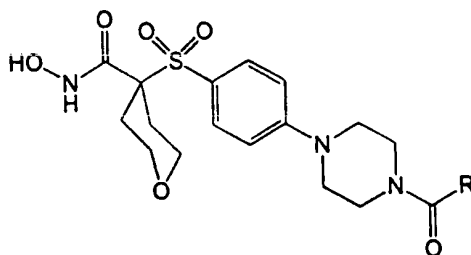
Step 12: Synthesis of Resin XII.

- 5 Into a fritted reaction vessel was placed resin VII (50 mg, 0.038 mmol) and cesium carbonate (122 mg, 0.38 mmol). A 0.43 M solution of the phenol in 1-methyl-2-pyrrolidinone (1 mL, 0.43 mmol) was added, then the vessel was capped under nitrogen.
- 10 The reaction mixture was agitated on a tabletop shaker and heated to 50 degrees Celsius for 48 hours. Then, the vessel was cooled to room temperature, and the resin was drained and washed with 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water,
- 15 water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

The following hydroxamic acids were synthesized from Resin IIIc using Step 11 with the

20 indicated isocyanate, followed by release from the polymer using the reaction conditions in Step 3.

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Example Number	Phenol	R	MS (FAB) m/z
295	phenol		490 (M+H)
296	3-methoxyphenol		520 (M+H)
297	4-chlorophenol		524.1 (M+H)
298	p-cresol		504.3 (M+H)
299	4-phenylphenol		566.3 (M+H)
300	4-hydroxy-diphenyl-methane		580.2 (M+H)

5

Example 301-323:Large Scale Preparation of Resin Xa

10

A fritted reaction vessel was charged with Resin IX (1 g, 0.86 mmol) and a 0.008 M solution of tetrakis-(triphenylphosphine)palladium(0) in ethylene glycol dimethyl ether (5 mL, 0.04 mmol). A 1 M solution of 2-formylbenzeneboronic acid in a 1:1

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mixture of ethanol and ethylene glycol dimethyl ether (6 mL, 6 mmol) was added followed by 1 M cesium carbonate in water (2 mL, 2 mmol). The vessel was sealed under argon and heated to 90 degrees Celsius for 16 hours. After this, the vessel was cooled to room temperature, and the resin drained and washed with the following sequence of solvents dimethylformamide, 1:1 dimethylformamide/water, dimethylformamide, water, methanol, methylene chloride (3X5 mL each solvent). The resin was dried in vacuo to yield 1.025 g of product as a tan polymeric solid. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 35 mg of Resin Xa as described in Step 3 yielded 11.2 mg of a tan solid

Large Scale Preparation of Resin Xb.

Preparation of Resin Xb followed the identical procedure described for preparation of resin Xa, except 3-formylbenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The yield after drying in vacuo was 1.052 g of Resin Xb as tan resin beads. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 20 mg of Resin Xb as described in Step 3 yielded 6.5 mg of a tan solid.

Large Scale Preparation of Resin Xc.

Preparation of Resin Xc followed the identical procedure described for preparation of resin Xa, except 4-formylbenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The yield after drying in vacuo was 1.03 g of Resin Xc as tan resin

-556-

beads. The theoretical loading of the polymer was 0.84 mmol/g. TFA cleavage performed on 28 mg of Resin Xb as described in Step 3 yielded 9.4 mg of a tan solid.

5

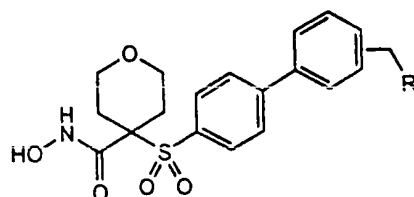
Step 13: Synthesis of Resin XIII.

Into a fritted reaction vessel was placed resin Xa, Xb or Xc (50 mg, 0.042 mmol). A 0.2 M solution of the amine in trimethylorthoformate (1 mL, 10 0.2 mmol) was added, and the vessel was capped under nitrogen. The reaction mixture was agitated on a tabletop shaker for 3 hours. Then, a 0.5 M solution of sodium triacetoxyborohydride in 1-methyl-2-pyrrolidinone (0.8 mL, 0.4 mmol) was added to the 15 vessel, and the mixture was agitated an additional 40 hours. After this, the resin was drained and washed (3X1 mL each solvent) with the following sequence of solvents: 1-methyl-2-pyrrolidinone, methanol, water, methanol and methylene chloride.

20

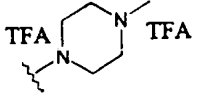
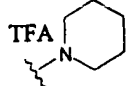
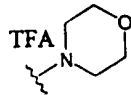
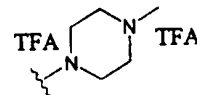
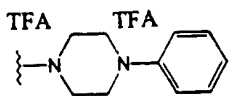
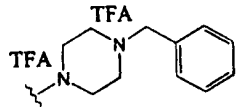
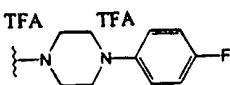
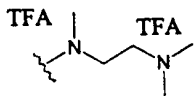
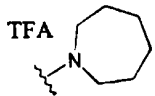
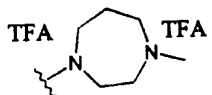

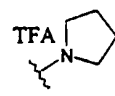

The following hydroxamic acids were synthesized using the indicated resin-bound aldehyde and the indicated amine following the procedure outlined in Step 13 followed by release from the polymer using 25 the procedure in Step 3:

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Example Number	Resin	Amine	R	position	MS (ES) m/z
301	Xb	1,2,3,4-tetrahydro-isoquinoline	TFA	3	507 (M+H)
302	Xb	1-methyl-piperazine	TFA	3	474 (M+H)
303	Xb	piperazine	TFA	3	460 (M+H)
304	Xb	benzylamine	TFA	3	481 (M+H)
305	Xb	propylamine	TFA	3	433 (M+H)
306	Xb	ethyl isonipecotate	TFA	3	531 (M+H)
307	Xa	benzylamine	TFA	2	481 (M+H)
308	Xa	isopropylamine	TFA	2	433 (M+H)
309	Xa	1,2,3,4-tetrahydro-isoquinoline	TFA	2	507 (M+H)

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310	Xa	1-methyl-piperazine		2	474 (M+H)
311	Xc	piperidine		4	459 (M+H)
312	Xc	morpholine		4	461 (M+H)
313	Xc	1-methyl-piperazine		4	474 (M+H)
314	Xc	1-phenyl-piperazine		4	536 (M+H)
315	Xc	1-benzyl-piperazine		4	550 (M+H)
316	Xc	1-(4-fluoro-phenyl)-piperazine		4	554 (M+H)
317	Xc	N,N,N'-trimethyl-ethylenediamine		4	476 (M+H)
318	Xc	hexamethyl-eneimine		4	473 (M+H)
319	Xc	1-methyl-homopiperazine		4	488 (M+H)
320	Xc	diethylamine		4	447 (M+H)
321	Xc	pyrrolidine		4	445 (M+H)
322	Xb	dimethylamine		3	419 (M+H)

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323	Xc	1-t-butoxy-carbonyl-piperazine		4	460 (M+H)
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Large Scale Preparation of Resin Xd

5 Preparation of Resin Xd followed the identical procedure described for preparation of resin Xa, except 4-carboxybenzeneboronic acid was substituted for 2-formylbenzeneboronic acid. The
10 yield after drying in vacuo was 1.07 g of Resin Xd as a tan polymeric solid. The theoretical loading of the polymer was 0.83 mmol/g. TFA cleavage performed on 23.5 mg of Resin Xd as described in Step 3 yielded
15 4.9 mg of a tan solid.

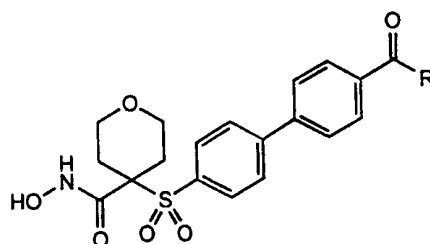
Step 14: Synthesis of Resin XIV

Into a fritted reaction vessel was placed resin Xd (50 mg, 0.042 mmol). The resin was washed
20 with 1-methyl-2-pyrrolidinone (2X3 mL), then a 1.0 M solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate in 1-methyl-2-pyrrolidinone (0.2 mL, 0.2 mmol) was added, followed
25 by a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) and a 1.0 M solution of the diisopropylethylamine in 1-methyl-2-pyrrolidinone (0.4 mL, 0.4 mmol). The vessel was
30 capped under nitrogen, and the reaction mixture was agitated on a tabletop shaker for 24 hours. Then, the resin was drained and washed with 1-methyl-2-pyrrolidinone (3X1 mL). The reaction with the amine was repeated by addition of a 1.0 M solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium

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hexafluorophosphate in 1-methyl-2-pyrrolidinone (0.2 mL, 0.2 mmol), a 0.7 M solution of the amine in 1-methyl-2-pyrrolidinone (0.3 mL, 0.21 mmol) and a 1.0 M solution of the diisopropylethylamine in 1-methyl-2-pyrrolidinone (0.4 mL, 0.4 mmol). The vessel was capped under nitrogen, and the reaction mixture was agitated an additional 8 hours. Then, the resin was drained and washed with the following sequence of solvents: 1-methyl-2-pyrrolidinone, 1:1 1-methyl-2-pyrrolidinone/water, water, 1:9 acetic acid/water, methanol, methylene chloride (3X1 mL each solvent).

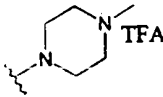


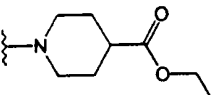
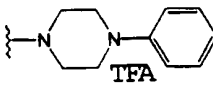
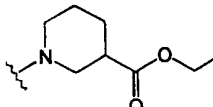
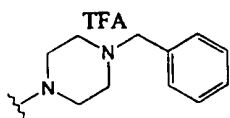
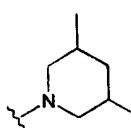
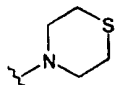
The following hydroxamic acids were synthesized using Resin Xd and the indicated amine following the procedure outlined in Step 14 followed by release from the polymer using the procedure in Step 3:



20

Example	amine	R	MS (ES) m/z
324	propylamine		447 (M+H)
325	piperidine		473 (M+H)
326	morpholine		475 (M+H)

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327	1-methyl-piperazine		488 (M+H)
328	diethylamine		461 (M+H)
329	pyrrolidine		459 (M+H)
330	ethyl isonipecotate		545 (M+H)
331	1-phenyl-piperazine		550 (M+H)
332	ethyl nipecotate		545 (M+H)
333	1-benzyl-piperazine		564 (M+H)
334	3,5-dimethyl-piperidine		501 (M+H)
335	thiomorpholine hydrochloride		491 (M+H)

Example 336: Preparation of 4-[[[4-[4-[[[9H-fluoren-9-ylmethoxy)carbonyl]amino]-1-piperidiny]]-phenyl] sulfonyl] tetrahydro-2H-pyran-4-carboxylic acid

Part A: To a solution of the product of Example 11, Part B (10.0 g, 34.7 mmol) in 1-methyl-2-pyrrolidinone (70 mL) was added 4-(N-t-

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butoxycarbonylamino)piperidine (10.43 g, 52.1 mmol), followed by diisopropylethylamine (6.0 mL, 34.7 mmol). The resulting mixture was heated at 80 degrees Celsius for 24 hours and then cooled to room temperature. The crude mixture was poured into 700 mL water, and the cloudy aqueous layer was extracted with ethyl acetate (3X150 mL). The combined organic layers were washed with 5% potassium hydrogen sulfate (2X150 mL) and brine (2X150 mL), dried over magnesium sulfate, and concentrated in vacuo to give the crude ester as a white foamy solid (13.04 g, 78%).

Part B: To a solution of the ester of part A (5.74 g, 11.9 mmol) in a mixture of ethanol (80 mL) and tetrahydrofuran (40 mL) was added 2 N sodium hydroxide (60 mL; 120 mmole). The resulting solution was heated to 60 degrees Celsius for 1 hour and then cooled to room temperature. The solution was concentrated in vacuo, and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The aqueous layer was separated and acidified with concentrated hydrogen chloride to pH 2. A white precipitate formed, which was collected by vacuum filtration and dried in vacuo to give the carboxylic acid as a white solid (4.88 g, 88%).

Part C: To a suspension of the carboxylic acid from part B (4.88 g, 10.4 mmol) in methylene chloride (35 mL) was added trifluoroacetic acid (35 mL), resulting in dissolution of the solid. After fifteen minutes at ambient temperature, the solution was concentrated in vacuo. The product was triturated with diethyl ether to give the amino acid as an off-white solid (4.92 g, 98%).

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Part D: A suspension of the amino acid from part C (4.92 g, 10.21 mmol) in a mixture of 10% sodium carbonate/water (35 mL), water (100 mL) and dioxane (100 mL) was cooled in an ice bath. To the cooled suspension is added a solution of 9-fluorenylmethylsuccinimidyl carbonate (3.79 g, 11.23 mmol) in dioxane (50 mL) dropwise. After complete addition, the ice bath was removed, and the mixture warmed to room temperature. After one hour, the solution was concentrated in vacuo, and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The aqueous layer was separated and acidified with concentrated hydrogen chloride to pH 2. The white precipitate formed, which was collected by vacuum filtration, washed with hexanes and dried in vacuo to give the title compound as a white solid (5.46 g, 91%).

Step 15: Preparation of Resin XVI.

Part A: Following the procedure outlined in Step 1 above, the product of Example 336 (2.4 g, 4.06 mmol) was reacted with Resin I (1.7 g, 2.03 mmol) to give Resin XV as a tan polymeric solid (2.82 g). Theoretical loading on polymer was 0.71 mmol/g.

Part B: Resin XV from part A above (2.76 g, 1.96 mmol) was suspended in a 1:4 piperidine/dimethylformamide solution (20 mL) in a fritted reaction vessel and agitated on a tabletop shaker for 5 minutes. The resin was drained, and an additional volume of a 1:4 mixture of piperidine/dimethylformamide (20 mL) was added to the vessel. The slurry was agitated at room temperature for 30 minutes. After this, the resin was drained

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and washed with dimethylformamide, methanol, and methylene chloride (3X20 mL each solvent). After drying in vacuo, the title resin was obtained as a tan polymeric solid (2.30 g).

5

Step 16: Acylation/Sulfonylation
of Resin XVI.

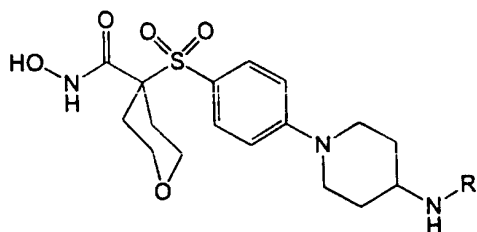
In a fritted reaction vessel, Resin XVI (50 mg, 0.043 mmol) was washed with 1-methyl-2-pyrrolidinone (2X1 mL). Then, a 0.22 M solution of the acylating or sulfonylating reagent in 1-methyl-2-pyrrolidinone (1 mL, 0.22 mmol) was added to the resin followed by diisopropylethylamine (40 uL, 0.22 mmol). The vessel was capped under nitrogen and agitated on a tabletop shaker at room temperature for 16 hours. Then, the resin was drained and washed with 1-methyl-2-pyrrolidinone, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

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The following hydroxamic acids were synthesized from Resin XVI using Step 16 with the indicated acylating or sulfonylating reagent, followed by release from the polymer using the reaction conditions in Step 3.

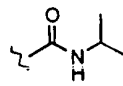
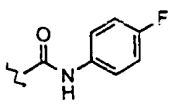
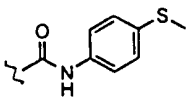
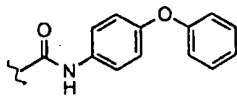
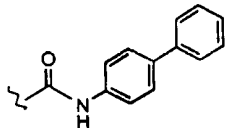
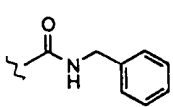
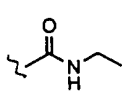
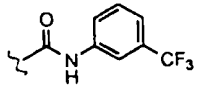
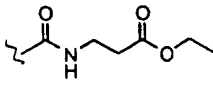
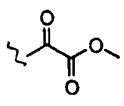
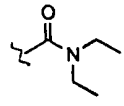
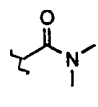
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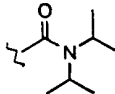
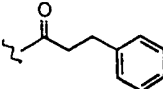
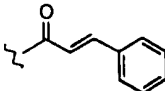
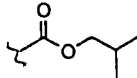
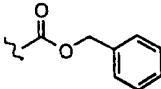
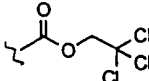
-565-



Example	Acylating or Sulfonylating Reagent	R	MS (ES) m/z
337	benzoyl chloride		488.2 (M+ H)
338	nicotinyl chloride-HCl	TFA	489.2 (M+ H)
339	benzenesulfonyl chloride		462 (M+H)
340	1-methyl- imidazole-4- sulfonyl chloride	TFA	528.2 (M+ H)
341	acetyl chloride		426.2 (M+ H)
342	methanesulfonyl chloride		462.1 (M+ H)
343	cyclohexyl isocyanate		509 (M+H)
344	2-methoxyphenyl isocyanate		533 (M+H)
345	phenyl isocyanate		503 (M+H)
346	beta-phenylethyl isocyanate		531 (M+H)

-566-

347	isopropyl isocyanate		469 (M+H)
348	4-fluorophenyl isocyanate		521 (M+H)
349	4-(methylthio)- phenyl isocyanate		549 (M+H)
350	4-phenoxyphenyl isocyanate		595 (M+H)
351	4-phenylphenyl isocyanate		579 (M+H)
352	benzyl isocyanate		517 (M+H)
353	ethyl isocyanate		455 (M+H)
354	alpha,alpha,alpha- trifluoro-m-tolyl isocyanate		571 (M+H)
355	ethyl 3-isocyanato- propionate		527 (M+H)
356	methyl oxalyl chloride		470 (M+H)
357	diethylcarbamyl chloride		483 (M+H)
358	dimethylcarbamyl chloride		455 (M+H)
359	diisopropyl carbamyl chloride		511 (M+H)

			
360	hydrocinnamoyl chloride		516 (M+H)
361	cinnamoyl chloride		514 (M+H)
361	isobutyl- chloroformate		484 (M+H)
363	benzylchloro- formate		518 (M+H) ,
364	trichloroethyl- chloroformate		558 (M+H)

Example 365-371:

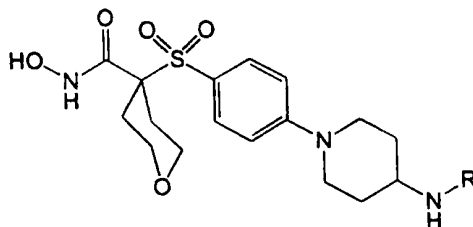
5 Step 17: Reductive Alkylation of
Resin XVI.

In a fritted reaction vessel, Resin XVI (50 mg, 0.043 mmol) was washed methylene chloride (2X1 mL). Then, a 1 M solution of the aldehyde or ketone in methylene chloride (1 mL, 1 mmol) was added to the resin. The vessel was capped under nitrogen and agitated on a tabletop shaker at room temperature for 3 hours. The resin was drained and washed with methylene chloride (3X1 mL). Then, the resin was retreated with the 1 M solution of the aldehyde or ketone in methylene chloride (1 mL, 1 mmol). The resin was drained and washed with methylene chloride (3X1 mL each solvent). Then, a 1 M solution of

-568-

sodium triacetoxyborohydride in 1-methyl-2-pyrrolidinone (1 mL, 1 mmol) was added to the resin, and the reaction was stirred overnight. After this, the resin was drained and washed with 1-methyl-2-pyrrolidinone, methanol, water, 1:9 acetic acid/water, methanol and methylene chloride (3X1 mL each solvent).

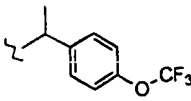
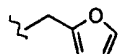
The following hydroxamic acids were synthesized from Resin XVI using Step 17 with the indicated aldehyde or ketone, followed by release from the polymer using the conditions in Step 3.



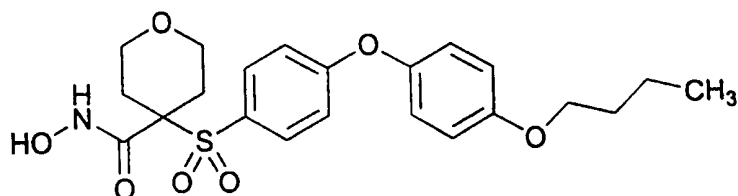
15

Example Number	Aldehyde or Ketone	R	MS (ES) m/z
365	butyraldehyde		440 (M+H)
366	acetone		426 (M+H)
367	N-propyl-4-pyridone		509 (M+H)
368	4-t-butylcyclohexanone		522 (M+H)
369	2-pyridine-carboxaldehyde		475 (M+H)

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370	4'-(trifluoromethoxy)-acetophenone		572 (M+H)
371	2-furaldehyde		464 (M+H)

Example 372: Preparation of 4-[[4-(4-butoxyphenoxy)-phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and 4-butoxyphenol (2.66 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for nineteen hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as an off-white foam (3.96 g, 93%). HRMS (ES+) M+NH₄⁺ calculated for C₂₇H₃₅N₁O₈ S₁F : 551.24, found 551.24.

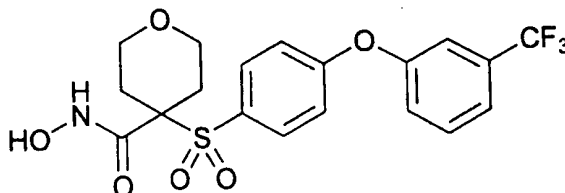
Part B: To a solution of the THP hydroxamate from part A (3.9 g, 7.3 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20

-570-

mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.75 g, 84%). HRMS (ES+) $\text{M} + \text{H}^+$ calculated for $\text{C}_{22}\text{H}_{27}\text{N}_1\text{O}_7\text{S}_1$: 450.16, found 450.16.

10

Example 373: Preparation of tetrahydro-N-hydroxy-4-
[[4-[3-(trifluoromethyl)phenoxy]phenyl]-
sulfonyl]-2H-pyran-4-carboxamide



15

Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and m-(trifluoromethyl)phenol (1.95 mL, 16 mmol). The slurry was stirred at ninety five degrees Celsius for nineteen hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.1 g, 97%). HRMS (ES+) $\text{M} + \text{H}^+$ calculated for $\text{C}_{24}\text{H}_{26}\text{N}_1\text{O}_7\text{S}_1\text{F}_3$: 530.15, found 530.14.

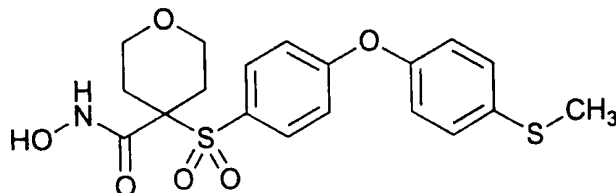
-571-

Part B: To a solution of the THP hydroxamate from part A (3.9 g, 7.4 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.9 g, 58%).

10 HRMS (ES+) M+ H⁺ calculated for C₁₉H₁₈N₁O₆S₁F₃ : 446.09, found 446.09.

Example 374: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(methylthio)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide

15



Part A: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and 4-(methylthio)phenol (2.24 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for twenty four hours. The reaction was concentrated in vacuo.

25 The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.1 g, 100%). HRMS (ES+)

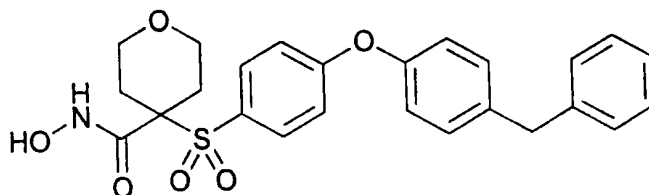
-572-

M+H⁺ calculated for C₂₄H₂₉N₁O₇ S₂: 508.15, found 508.15.

Part B: To a solution of the THP hydroxamate from part A (4.0 g, 7.9 mmol) in 1,4-dioxane (20 mL) was added 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.9 g, 57%).

HRMS (ES+) M+ H⁺ calculated for C₁₉H₂₁N₁O₆S₂ : 424.09, found 424.09.

15 Example 375: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(phenylmethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide



20

Part A: To a solution of the product of Example 55 (2.7 g, 7 mmol) in dimethylacetamide (15 mL) was added cesium carbonate (6.84 g, 21 mmol) and 4-hydroxydiphenylmethane (2.8 g, 14 mmol). The slurry was stirred at ninety degrees Celsius for nineteen hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica,

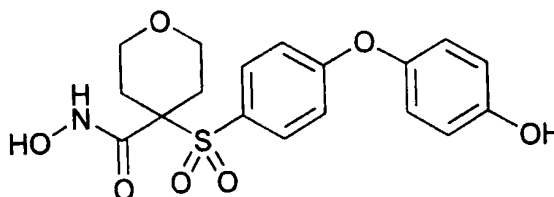
-573-

ethyl acetate/hexanes) provided the substituted THP hydroxamate as a light yellow foam (3.7 g, 96%). HRMS (ES+) $M+H^+$ calculated for $C_{30}H_{33}N_1O_7$ S_1 : 552.21, found 552.21.

5 Part B: To a solution of the THP hydroxamate from part A (3.5 g, 6.4 mmol) in 1,4-dioxane (16 mL) was added 4N HCl dioxane solution (16 mL) and methanol (16 mL). After fifteen minutes at ambient temperature the reaction was diluted with
10 ethyl acetate and washed with water, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (1.95 g, 67%).
HRMS (ES+) $M+H^+$ calculated for $C_{25}H_{25}N_1O_6S_1$:
15 468.15, found 468.15.

Example 376: Preparation of tetrahydro-N-hydroxy-4-
[[4-(4-hydroxyphenoxy)phenyl]sulfonyl]-
2H-pyran-4-carboxamide

20



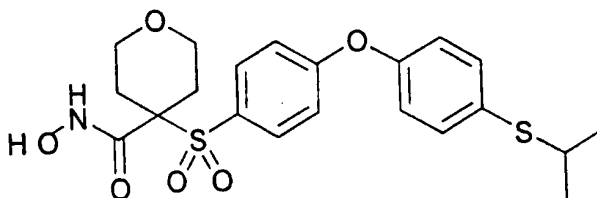
Part A: To a solution of the product of
Example 55) (2.7 g, 7 mmol) in dimethylacetamide (20
25 mL) was added cesium carbonate (6.84 g, 21 mmol) and
4-(benzyloxy)phenol (2.8 g, 14 mmol). The slurry was
stirred at ninety five degrees Celsius for six hours.
The reaction was concentrated in vacuo. The residue
was taken up in ethyl acetate, washed with brine,

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dried over Na_2SO_4 , filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (3.94 g, 99%). HRMS (ES+) $\text{M} + \text{NH}_4^+$ calculated for $\text{C}_{30}\text{H}_{33}\text{N}_1\text{O}_8$ S_1 : 585.23, found 585.23.

Part B: To a solution of the THP hydroxamate from part A (1.5 g, 2.64 mmol) in glacial acetic acid (5 mL) was added concentrated HCl (5 mL) and the reaction was heated to sixty degrees Celsius for twenty minutes. The reaction was cooled, diluted with water (100 mL) and extracted with ethyl acetate. The ethyl acetate extract was washed with water three times, brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (810 mg, 78%). HRMS (ES+) $\text{M} + \text{NH}_4^+$ calculated for $\text{C}_{18}\text{H}_{19}\text{N}_1\text{O}_7\text{S}_1$: 468.15, found 468.15.

Example 377: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-[(1-methylethyl)thio]phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a suspension of 4-hydroxythiophenol (5.0 g, 40 mmol) and potassium

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carbonate (8.0 g, 58 mmol) in dimethylformamide (70 mL) was added 2-iodopropane (7.0 g, 41 mmol). The slurry was stirred at ambient temperature for one hour. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed two times with water, 10% HCl solution, brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted phenol as a clear colorless oil (5.1 g, 76%).

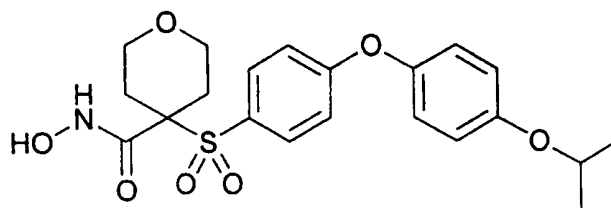
Part B: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and the phenol from part A (2.7 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for fifteen hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as a white foam (4.15 g, 97%). HRMS (ES+) $\text{M} + \text{H}^+$ calculated for $\text{C}_{26}\text{H}_{33}\text{N}_1\text{O}_7$ S_2 : 536.18, found 538.17.

Part C: To a solution of the THP hydroxamate from part A (3.9 g, 7.3 mmol) in 1,4-dioxane (18 mL) was added 4N HCl dioxane solution (18 mL) and methanol (18 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as an off white solid (2.32 g,

-576-

71%). HRMS (ES+) $M+H^+$ calculated for $C_{21}H_{25}N_1O_6S_2$:
452.12, found 452.12.

5 Example 378: Preparation of tetrahydro-N-hydroxy-4-
[[4-[4-(1-methylethoxy)phenoxy]phenyl]-
sulfonyl]-2H-pyran-4-carboxamide



10 Part A: To a solution of benzoic acid, 4-
hydroxyphenylester (8.57 g, 40 mmol) in
dimethylacetamide (65 mL) was added potassium
carbonate (8.3 g, 60 mmol) and 2-iodopropane (5 mL,
50 mmol). The slurry was stirred at sixty five
degrees Celsius for one hour. The reaction was
15 concentrated in vacuo. The residue was taken up in
ethyl acetate, washed with water three times, brine,
dried over Na_2SO_4 , filtered, and concentrated in vacuo
to yield the isopropoxy compound as a light gray
solid (9.7g, 95%).

20 Part B: To a slurry of the isopropoxy
compound from part A (9.7 g, 38 mmol) in 1,4-dioxane
(20 mL) and water (20 mL) was added 2.5N sodium
hydroxide solution (26 mL, 65 mmol). The slurry was
stirred at sixty degrees Celsius for four hours. The
25 reaction was cooled and 6N hydrochloric acid solution
was added until the pH=5. The reaction was extracted
with methylene chloride. The organic layer was
washed with 5% ammonium hydroxide solution four
times, water, brine, dried over Na_2SO_4 , filtered, and

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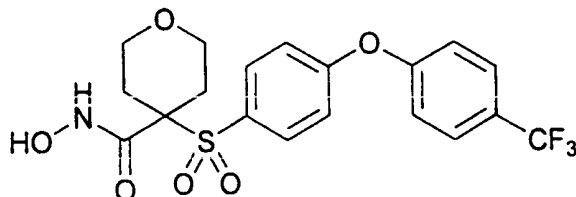
concentrated in vacuo to yield the phenol as an amber oil (5.4 g, 94%).

Part C: To a solution of the product of Example 55 (3.1 g, 8 mmol) in dimethylacetamide (20 mL) was added cesium carbonate (7.28 g, 24 mmol) and the phenol from part B (2.4 g, 16 mmol). The slurry was stirred at ninety five degrees Celsius for twenty one hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP hydroxamate as an off white foam (3.65 g, 88%). HRMS (ES+) M+ H⁺ calculated for C₂₆H₃₃N₁O₈ S₁ : 520.20, found 520.20.

Part D: To a solution of the THP hydroxamate from part C (3.5 g, 6.7 mmol) in 1,4-dioxane (17 mL) was added 4N HCl dioxane solution (17 mL) and methanol (17 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as an off white solid (2.2 g, 80%). HRMS (ES+) M+ H⁺ calculated for C₂₁H₂₅N₁O₇S₁ : 436.14, found 436.14.

Example 379: Preparation of tetrahydro-N-hydroxy-4-
[[4-[4-[(trifluoromethyl)phenoxy]-
phenyl]-sulfonyl]-2H-pyran-4-
carboxamide

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Part A: In dry equipment under nitrogen, sodium hydride (60% oil dispersion) (11. g, 0.275
5 mol) was added to a solution of 4-[4-(trifluoromethyl)phenoxy]-phenol (50.0 g, 0.197 mol) in dry dimethylformamide (150 mL) at zero degrees Celsius. After fifteen minutes, a solution of dimethylthiocarbamoyl chloride (32.0 g, 0.259 mol) in
10 dry dimethylformamide (100 mL) was added. The reaction was stirred at ambient temperature for sixteen hours. The reaction was poured onto 10% hydrochloric acid solution (1 L). Vacuum filtration of the resulting precipitate provided the thiono
15 compound as a white solid (67.0 g, 100%).

Part B: The thiono compound from part A (70 g, 0.2 mol) was heated to three hundred seventeen degrees Celsius for thirty minutes behind a safety shield. The reaction exothermed to three hundred
20 thirty degrees Celsius. The heat was removed and the reaction came to ambient temperature to yield the thiocarbamate as a brown solid (70 g, 100%).

Part C: To a solution of the thiocarbamate from part B (65.0 g, 0.19 mol) in methanol (510 mL)
25 with a subsurface nitrogen stream was added 2.5N sodium hydroxide solution (160 mL, 0.4 mol). The slurry was stirred at seventy four degrees Celsius for two hours. The reaction was cooled and the methanol removed in vacuo. The residue was diluted

-579-

with water (100 mL) and extracted with diethyl ether four times. A subsurface stream of nitrogen was added to the aqueous solution and sodium chloroacetate (22.2 g, 0.19 mol) was added. The reaction was stirred at an ambient temperature and after thirty minutes the nitrogen stream was removed. After twelve hours, the solution was cooled and 6N hydrochloric acid was added until the pH=1. The slurry was extracted with ethyl acetate four times. The combined ethyl acetate extracts were washed with 0.1N hydrochloric acid, water, brine, dried over Na₂SO₄, filtered and dried in vacuo to give the thioacetic acid as a tan solid (61.0 g, 98%).

Part D: To a solution of the thioacetic acid from part C (54.45g, 0.166 mol) in tetrahydrofuran (370 mL) was added water (45 mL) and Oxone® (306 g, 0.498 mol) at twenty degrees Celsius. An exotherm to forty two degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with tetrahydrofuran and then water (250 mL) was added to the filtrate. The filtrate was concentrated in vacuo. The slurry was extracted with ethyl acetate four times. The combined extracts were washed with water three times, brine, dried over MgSO₄, filtered, and concentrated in vacuo to give the sulfone as a beige solid (60.0 g, 100%).

Part E: A solution of the sulfone from part D (119.52 g, 0.332 mol) in methanol (660 mL) and 4N hydrochloric acid in dioxane solution (20 mL) was stirred at ambient temperature for twelve hours. The reaction was heated to a boil and cooled slowly to ambient temperature. The resulting crystals were

-580-

filtered, washed well with cold methanol, and dried to give the methyl ester as a white solid (89.4 g, 72%).

Part F: To a solution of the methyl ester
5 from part E (64.5 g, 0.180 mol) in dimethylacetamide (360 mL) was added potassium carbonate (66.8 g, 0.48 mol), bis-(2-bromoethyl)ether (40 mL, 0.305 mol), 4-dimethylaminopyridine (1.1 g, 9 mmol), and tetrabutylammonium bromide (2.9 g, 9 mmol). The
10 reaction was stirred overnight at ambient temperature. The reaction was slowly poured into 1N HCl (500 mL). The resulting precipitate was filtered, washed with water, then hexanes. The solid was recrystallized from methanol to give the pyran
15 compound as a white solid (62.8 g, 79%). MS (ES+) $M+NH_4^+$ calculated for $C_{20}H_{19}O_5S_1F_3$: 462.12, found 462.12.

Part G: In dry equipment under nitrogen, the pyran compound from part F (64.0 g, 0.144 mol)
20 was dissolved in dry tetrahydrofuran (250 mL) and a solution of potassium trimethylsilonate (55.9 g, 0.432 mol) in dry tetrahydrofuran (40 mL) was added at ambient temperature. After two hours, water (200 mL) was added and the solution concentrated in vacuo.
25 The slurry was extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, brine, dried over Na_2SO_4 ,
30 filtered, and concentrated in vacuo. The residue was heated in diethyl ether, the resulting solid filtered and dried to give the carboxylic acid as a white

-581-

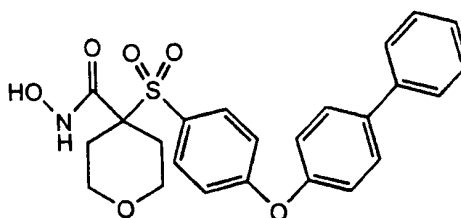
solid (56.3 g, 91%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{19}H_{17}O_6 S_1F_3$: 448.10, found 448.10.

Part H: In dry equipment under nitrogen, the carboxylic acid from part G (49.0 g, 0.114 mol) was dissolved in dry dimethylformamide (280 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (18.5 g, 0.137 mol), N-methylmorpholine (37.5 mL, 0.342 mol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (41.3 g, 0.353 mol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 30.6 g, 0.160 mol). After four hours at ambient temperature, the reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo to give the THP hydroxamate as a white foam (62.6 g, 100%). HRMS (ES+) $M+NH_4^+$ calculated for $C_{24}H_{26}NO_7S_1F_3$: 547.17, found 547.17.

Part I: To a solution of the THP hydroxamate from part H (58.5 g, 0.11 mol) in 1,4-dioxane (280 mL) was added 4N HCl dioxane solution (280 mL) and methanol (280 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (42.79 g, 87%) HRMS (ES+) $M+NH_4^+$ calculated for $C_{19}H_{18}NO_6S_1F_3$: 463, found 463.

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Example 380: Preparation of 4-[[4-([1,1'-biphenyl]-4-yloxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



5

Part A: To a solution of the product of Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (8 mL) was added 4-phenylphenol (Aldrich, 1.3 g, 7.8 mmol) followed by cesium carbonate (6.8 g, 20.8 mmol). The reaction was heated at ninety-five degrees Celsius for five hours. Stripping the dimethylacetamide in vacuo afforded a brown solid (5.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected biphenyl product in solution.

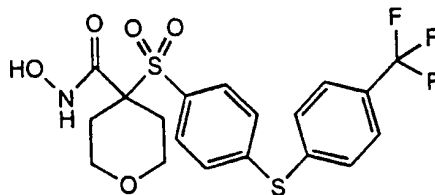
Part B: To the collected THP-protected diphenyl product from A in acetonitrile/ water (50 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a white solid (2.0 g, 83%). MS (FAB) M⁺H calculated for C₂₄H₂₃NO₆S: 454, found 454.

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-583-

Example 381: Preparation of tetrahydro-N-hydroxy-4-
[[4-[[4-(trifluoromethyl)phenyl]thio]
phenyl]-sulfonyl]-2H-pyran-4-
carboxamide

5



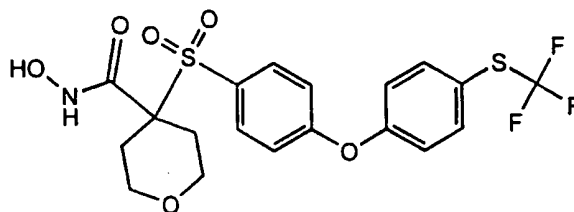
Part A: To a solution of the product of
Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6
10 mL) was added 4-trifluoromethylthiophenol (Maybridge,
2.0 g, 11.2 mmol), followed by potassium carbonate
(2.9 g, 20.8 mmol). The reaction was heated at
sixty-five degrees Celsius for twelve hours.
Stripping the dimethylacetamide in vacuo afforded a
15 brown solid (6.5 g, quantitative). Chromatography
(reverse phase, C-18, acetonitrile/water) gave the
THP-protected trifluoromethyl product in solution.

Part B: To the solution of the crude THP-
protected trifluoromethyl product from in
20 acetonitrile/water (40 mL) was slowly added 10% HCl_{aq}
(100 mL). After stirring overnight (about eighteen
hours), the acetonitrile was stripped. The resultant
precipitate was collected, giving the title compound
as a tan solid (0.75 g, 31 %). MS (FAB) M⁺H
25 calculated for C₁₉H₁₈F₃NO₅S₂: 462, found 462.

-584-

Example 382: Preparation of Tetrahydro-N-hydroxy-4-
[[4-[4-[(trifluoromethyl)thio]phenoxy]
phenyl]-sulfonyl]-2H-pyran-4-
carboxamide

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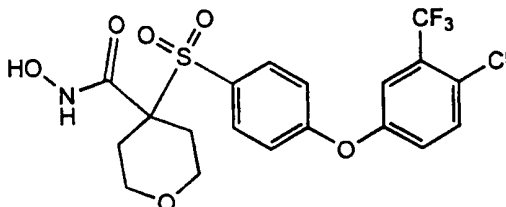
Part A: To a solution of the product of
10 Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6
mL) was added 4-(trifluoromethylthio)thiophenol
(Aldrich, 1.5 g, 7.8 mmol) followed by cesium
carbonate (6.8 g, 20.8 mmol). After adding a
catalytic amount of potassium fluoride, the reaction
15 was heated at ninety-five degrees Celsius for twelve
hours. Stripping the dimethylacetamide in vacuo
afforded a brown solid (7.2 g, quantitative).
Chromatography (reverse phase, C-18,
acetonitrile/water) gave the THP-protected
20 trifluoromethylthio product in solution.

Part B: To the solution of the crude THP-
protected trifluoromethylthio product from A in
acetonitrile/water (40 mL) was slowly added 10% HCl_{aq}
(100 mL). After stirring overnight (about eighteen
25 hours), the acetonitrile was stripped. The resultant
precipitate was collected, giving the title compound
as a tan solid (0.60 g, 24 %). MS (FAB) M⁺H
calculated for C₁₉H₁₈F₃NO₆S₂: 476, found 476.

-585-

Example 380: Preparation of 4-[[4-[4-chloro-3-(trifluoro-methyl)phenoxy]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

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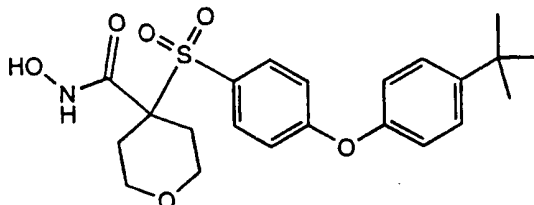
Part A: To a solution of the product of
10 Example 55 (2.0 g, 5.2 mmol) in dimethylacetamide (6 mL) was added 4-chloro-3-trifluoromethylphenol (Avocado, 1.5 g, 7.8 mmol) followed by cesium carbonate (6.8 g, 20.8 mmol). The reaction was heated at ninety-five degrees Celsius for twelve
15 hours. Stripping the dimethylacetamide in vacuo afforded a brown solid (7.6 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

20 Part B: To the solution of the crude THP-protected product from in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was
25 collected, giving the title compound as a white solid (0.92 g, 37 %). MS (FAB) M⁺H calculated for C₁₉H₁₇ClF₃NO₆S: 480, found 480.

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Example 384: Preparation of 4-[[4-[4-(1,1-dimethylethyl)-phenoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

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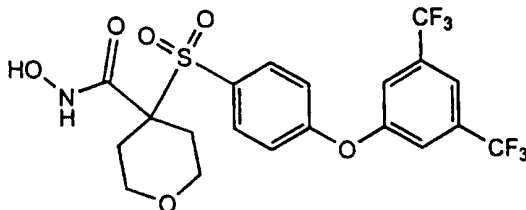
Part A: To a solution of the product of
10 Example 55 (5.0 g, 12.9 mmol) in dimethylacetamide
(25 mL) was added 4-t-butylphenol (Avocado, 2.9 g,
19.4 mmol) followed by cesium carbonate (20.4 g,
20.862.5 mmol). The reaction was heated at ninety-
five degrees Celsius for twelve hours. Stripping the
15 dimethylacetamide in vacuo afforded a brown solid
(9.4 g, quantitative). Chromatography (reverse
phase, C-18, acetonitrile/water) gave the THP-
protected product in solution.

Part B: To the solution of the crude THP-
20 protected product from in acetonitrile/water (60 mL)
was slowly added 10% HCl_{aq} (100 mL). After stirring
overnight (about eighteen hours), the acetonitrile
was stripped. The resultant precipitate was
collected, giving the title compound as a white solid
25 (0.28 g, 5 %). MS (FAB) M⁺H calculated for C₂₂H₂₇NO₆S:
434, found 434.

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Example 385: Preparation of 4-[[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

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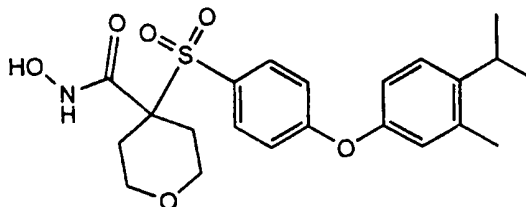
Part A: To a solution of the product of
10 Example 55 (3.0 g, 7.7 mmol) in dimethylacetamide
(15 mL) was added 3,5-ditrifluoromethylphenol (2.9 g,
19.4 mmol) followed by cesium carbonate (20.4 g,
20.862.5 mmol). The reaction was heated at ninety-
five degrees Celsius for twelve hours. Stripping the
15 dimethylacetamide in vacuo afforded a brown solid
(14.7 g, quantitative). Chromatography (reverse
phase, C-18, acetonitrile/water) gave the THP-
protected product in solution.

Part B: To the solution of the crude THP-
20 protected product from in acetonitrile water (60 mL)
was slowly added 10% HCl_{aq} (100 mL). After stirring
overnight (about eighteen hours), the acetonitrile
was stripped. The resultant precipitate was
collected, giving the title compound as a white solid
25 (1.2 g, 31 %). MS (FAB) M⁺H calculated for C₂₀H₁₇
F₆NO₆S: 514, found 514.

-588-

Example 386: Preparation of tetrahydro-N-hydroxy-4-[[4-[3-methyl-4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide

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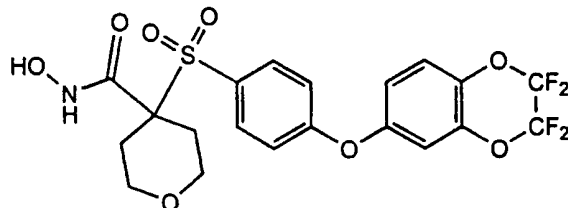
Part A: To a solution of the product of Example 55 (4.0 g, 10.3 mmol) in dimethylacetamide
10 (20 mL) was added 4-isopropyl-3-methylphenol (Aldrich, 2.3 g, 15.5 mmol) followed by cesium carbonate (16.8 g, 51.5 mmol). The reaction was heated at ninety-five degrees Celsius for twelve hours. Stripping the dimethylacetamide in vacuo
15 afforded a brown solid (18.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected product in solution.

Part B: To the solution of the crude THP-
20 protected product from A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about eighteen hours), the acetonitrile was stripped. The resultant precipitate was collected, giving the title compound as a tan
25 solid (1.8 g, 40 %). MS (FAB) M⁺H calculated for C₂₂H₂₇F₃NO₆S: 432, found 432.

-589-

Example 387: Preparation of Tetrahydro-N-hydroxy-4-
[[4-[(2,2,3,3-tetrafluoro-2,3-dihydro-
1,4-benzodioxin-6-yl)oxy]phenyl]
sulfonyl]-2H-pyran-4-carboxamide

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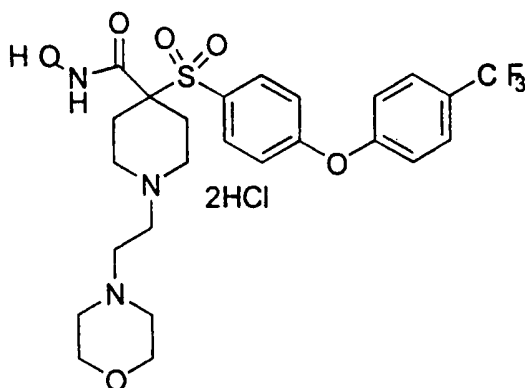


Part A: To a solution of the product of
Example 55 (5.0 g, 12.9 mmol) in dimethylacetamide
10 (25 mL) was added 2,2,3,3-tetrafluoro-6-
hydroxybenzodioxene (Oakwood, 4.3 g, 19.4 mmol)
followed by cesium carbonate (21.0 g, 64.5 mmol).
The reaction was heated at ninety-five degrees
Celsius for five hours. Stripping the
15 dimethylacetamide in vacuo afforded a brown solid
(11.3 g, quantitative) Chromatography (reverse
phase, C-18, acetonitrile/water) gave the THP-
protected product in solution.

Part B: To the collected THP-protected
20 product from A in acetonitrile/water (50 mL) was
slowly added 10% HCl_{aq} (100 mL). After stirring
overnight (about eighteen hours), the acetonitrile
was stripped. The resultant precipitate was
collected, giving the title compound as a white
25 solid (3.5 g, 54%). MS (FAB) M⁺H calculated for
C₂₀H₁₇F₄NO₈S: 506, found 506.

-590-

Example 388: Preparation of N-hydroxy-1-[2-(4-morpholinyl)-ethyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-phenyl]sulfonyl]-4-piperidinecarboxamide, dihydrochloride



Part A: To a suspension of 4-bromopiperidine
10 hydrobromide (107.0 g, 0.436 mol) in tetrahydrofuran
(1 L) was slowly added triethylamine (122 mL, 0.872
mol) followed by di-tert-butyl dicarbonate (100 g,
0.458 mol), which was added in several portions. The
resulting mixture was stirred at ambient temperature
15 for 22 hours then filtered and concentrated in vacuo.
The solids were washed with hexanes and then
collected by filtration to give the Boc-piperidine
compound as an amber oil (124 g, >100 %).

Part B: To a solution of 4-fluorophenol (50.0
20 g, 0.390 mol) in acetone (400 mL), degassed with N₂,
was added Cs₂CO₃ (159 g, 0.488 mol). After degassing
the resulting mixture with N₂ for 5 minutes, the Boc-
piperidine compound of part A (85.9 g, 0.325 mol) was
added. The resulting mixture was stirred at ambient
25 temperature for 18 hours and then filtered through a

-591-

pad of Celite®, washing with acetone. The filtrate was concentrated in vacuo to provide the sulfide as a tan residue (98.5 g, 97%).

Part C: To a solution of the sulfide of part B
5 (8.00 g, 25.7 mmol) in dichloromethane (90 mL) and methanol (15 mL) was added monoperoxyphthalic acid magnesium salt hexahydrate (19.1 g, 38.6 mmol) in two portions. The resulting mixture was stirred at ambient temperature for 1.5 hours and then filtered.
10 The filtrate was washed with saturated NaHCO₃ and then with saturated NaCl. The combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated in vacuo. The resulting solids
15 were washed with hexanes then dissolved in dichloromethane and filtered through a pad of Celite®, washing with dichloromethane. The filtrate was concentrated in vacuo and recrystallization from ethyl acetate provided the sulfone as a white
20 crystalline solid (4.45 g, 50%).

Part D: To a solution of sulfone of part C (7.00 g, 20.4 mmol) in N,N-dimethylformamide (40 mL) was added Cs₂CO₃ (19.9 g, 61.2 mmol) and α,α,α -trifluoro-p-cresol (3.97 g, 24.5 mmol). The
25 resulting mixture was heated at eighty degrees Celsius for 16 hours. After cooling to ambient temperature the reaction mixture was concentrated in vacuo. The resulting residue was treated with H₂O and the solids were collected by filtration. The solids
30 were then washed with hexanes then methanol to provide the biaryl ether as a tan solid (8.60 g, 87%).

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Part E: To a solution of the biaryl ether of part D (8.59 g, 17.7 mmol) in tetrahydrofuran (100 mL), cooled to zero degrees Celsius, was slowly added lithium bis(trimethylsilyl)amide (22.0 mL, 1.0M in tetrahydrofuran, 22.0 mmol), at such a rate that the temperature of the reaction never exceeded one degree Celsius. The resulting mixture was stirred at zero degrees Celsius for 1 hour then a solution of methyl chloroformate (2.05 mL, 26.6 mmol) in tetrahydrofuran (5.0 mL) was slowly added, at such a rate that the temperature of the reaction mixture never exceeded four degrees Celsius. After the addition was complete, the mixture was slowly permitted to warm to ambient temperature. Saturated NH_4Cl (50 mL) was added and the tetrahydrofuran was removed in vacuo. Water (50 mL) was added to the residue which was then extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4 . Recrystallization from methanol provided the methyl ester as a pale yellow crystalline solid (7.66 g, 80%).

Part F: To a solution of the methyl ester of part E (7.66 g, 14.1 mmol) in dioxane (30 mL) and methanol (10 mL) was added a solution of 4N HCl in dioxane (10 mL, 40 mmol). After stirring at ambient temperature for 2 hours additional 4N HCl in dioxane (10 mL, 40 mmol) was added. After stirring at ambient temperature for 2.5 hours, the reaction mixture was concentrated in vacuo to provide the amine as an off-white solid (6.80 g, >100%).

Part G: To a suspension of the amine of part F (3.00 g, 6.25 mmol) in acetonitrile (20 mL) was added K_2CO_3 (3.46 g, 25.0 mmol), 4-(2-chloroethyl)morpholine

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hydrochloride (1.22 g, 6.56 mmol) and a catalytic amount of NaI. The resulting mixture was heated at reflux for 22 hours. After cooling to ambient temperature, the reaction mixture was filtered
5 through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated in vacuo to provide the morpholinyl ethyl amine as a tan solid (3.45 g, >100%).

Part H: To a solution of the morpholinyl ethyl
10 amine of part G (3.45 g, 6.25 mmol) in tetrahydrofuran (60 mL) was added potassium trimethylsilanolate (1.60 g, 12.50 mmol). After stirring at ambient temperature for 25 hours, H₂O was added. The reaction mixture was then neutralized (pH
15 7) with 1N HCl. The tetrahydrofuran was removed in vacuo and the resulting precipitate was collected by filtration and washed with diethyl ether to provide the amino acid as an off-white solid (2.87 g, 85%).

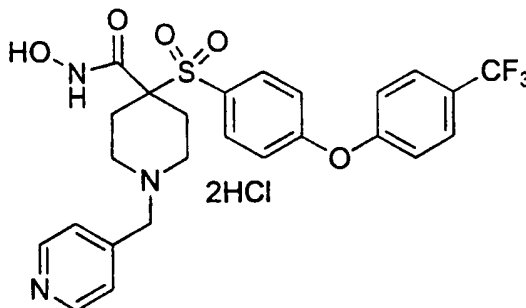
Part I: To a suspension of the amino acid of
20 part H (2.87 g, 5.29 mmol) in dichloromethane (25 mL) was added N-methylmorpholine (1.74 mL, 15.9 mmol), O-(tetrahydropuranyl) hydroxylamine (0.682 g, 5.82 mmol) and PyBroP® (2.96 g, 6.35 mmol). After stirring at ambient temperature for 19 hours
25 additional N-methylmorpholine (0.872 mL, 7.94 mmol), O-(tetrahydropuranyl) hydroxylamine (0.310 g, 2.65 mmol) and PyBroP® (1.48 g, 3.17 mmol) were added. The resulting mixture was stirred at ambient
30 temperature for 3 hours and then concentrated in vacuo. The residue was partitioned between ethyl acetate and H₂O. The organic layers were washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, methanol/chloroform) provided the

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protected hydroxamate as an off-white solid (2.62 g, 77%).

Part J: To a solution of the protected hydroxamate of part I (2.62 g, 4.08 mmol) in dioxane (9 mL) and methanol (3 mL) was added a solution of 4N HCl in dioxane (10 mL, 40.0 mmol). The resulting mixture was stirred at ambient temperature for 2 hours and then diethyl ether (20 mL) was added. The resulting solids were collected by filtration to give the title compound as an off-white solid (2.31 g, 90%). MS MH^+ calculated for $C_{25}H_{31}O_6N_3SF_3$: 558, found 558.

Example 389: Preparation of N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-(4-(trifluoromethyl)phenoxy]phenyl)sulfonyl]-4-piperidinecarboxamide, dihydrochloride



20

Part A: To a suspension of the amine of part F, Example 388 (1.50 g, 3.13 mmol) in acetonitrile (10 mL) were added K_2CO_3 (1.73 g, 12.5 mmol) and 4-picolyl chloride hydrochloride (0.565 g, 3.44 mmol). After stirring at reflux for 21.5 hours, the reaction mixture was filtered through a pad of Celite®,

-595-

washing with ethyl acetate. The filtrate was concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the picolyl amine as a clear gum (1.44 g, 86%).

5 Part B: To a solution of the picolyl amine of part A (1.44 g, 2.69 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.690 g, 5.38 mmol). The resulting mixture was stirred at ambient temperature for 20 hours and then the
10 tetrahydrofuran was removed by blowing N₂ over the reaction mixture. Water (8 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration to provide the amino acid as a white solid (1.31 g,
15 94%).

 Part C: To a suspension of the amino acid of part B (1.31 g, 2.52 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.408 g, 3.02 mmol), N-methylmorpholine (0.831 mL, 7.56 mmol),
20 O-(tetrahydropuranyl) hydroxylamine (0.443 g, 3.78 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.676 g, 3.53 mmol). The resulting mixture was stirred at ambient temperature for 3 days then concentrated in vacuo.
25 The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as
30 a white foam (1.24 g, 79%).

 Part D: To a solution of the protected hydroxamate of part C (1.24 g, 2.00 mmol) in dioxane (6 mL) and methanol (2 mL) was added a solution of 4N

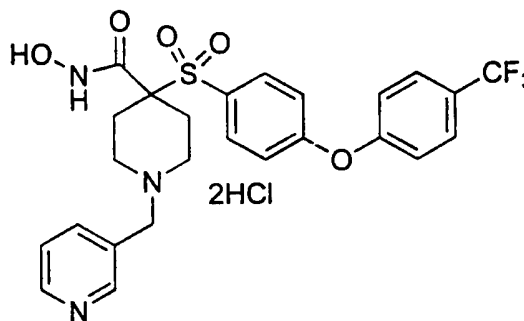
-596-

HCl in dioxane (5.00 mL, 20.0 mmol). After stirring at ambient temperature for 2.5 hours the reaction mixture was concentrated in vacuo. The resulting foam was then treated again with a solution of 4N HCl in dioxane (3 mL) for 15 minutes then diethyl ether was added and the resulting precipitate was collected by filtration to provide the title compound as an off-white solid (1.04 g, 85%). MS MH^+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

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Example 390: Preparation of N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride

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Part A: To a suspension of the amine of part F, Example 388 (1.00 g, 2.08 mmol) in acetonitrile (10 mL) was added K_2CO_3 (1.15 g, 8.33 mmol) and 3-picolyl chloride hydrochloride (0.375 g, 2.29 mmol). After stirring at reflux for 12 hours, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated in vacuo. Chromatography (on silica, ethyl

25

-597-

acetate/hexanes) provided the picolyl amine as a pale yellow foam (0.740 g, 67%).

Part B: To a solution of the picolyl amine of part A (0.740 g, 1.38 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.355 g, 2.77 mmol). The resulting mixture was stirred at ambient temperature for 17 hours, then additional potassium trimethylsilanolate (0.044 g, 0.343 mmol) was added and the resulting mixture was stirred at ambient temperature for 2 hours. The tetrahydrofuran was removed by blowing N₂ over the reaction mixture. Water (5 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration and dried by concentration in vacuo with acetone to provide the amino acid as an off-white solid (0.700 g, 97%).

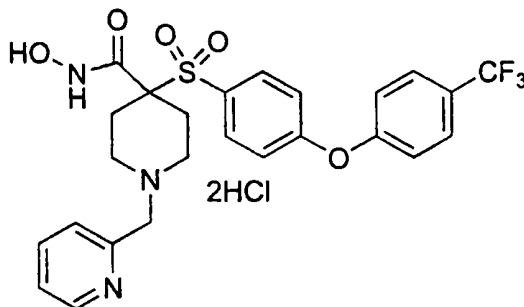
Part C: To a suspension of the amino acid of part B (0.700 g, 1.34 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.218 g, 1.61 mmol), N-methylmorpholine (0.442 mL, 4.02 mmol), O-(tetrahydropuranyl) hydroxylamine (0.235 g, 2.01 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.360 g, 1.88 mmol). The resulting mixture was stirred at ambient temperature for 23 hours, then concentrated in vacuo. The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as an off-white foam (0.500 g, 60%).

Part D: To a solution of the protected hydroxamate of part C (0.500 g, 0.807 mmol) in

-598-

dioxane (1.5 mL) and methanol (0.5 mL) was added a solution of 4N HCl in dioxane (3.0 mL, 12.00 mmol). After stirring at ambient temperature for 2 hours, diethyl ether was added and the resulting precipitate
5 was collected by filtration to provide the title compound as a yellow solid (0.363 g, 74%). MS MH^+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

Example 391: Preparation of N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide,
10 dihydrochloride



Part A: To a suspension of the amine of part F, Example 388 (1.26 g, 2.63 mmol) in acetonitrile (10 mL) was added K_2CO_3 (1.45 g, 10.5 mmol) and 2-picolyl
20 chloride hydrochloride (0.475 g, 2.89 mmol). After stirring at reflux for 12 hours, the reaction mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated in vacuo. Chromatography (on silica, ethyl
25 acetate/hexanes) provided the picolyl amine as an amber oil (1.40 g, 99%).

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Part B: To a solution of the picolyl amine of part A (1.40 g, 2.62 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.672 g, 5.24 mmol). The resulting mixture was stirred at
5 ambient temperature for 15 hours. The tetrahydrofuran was removed by blowing N₂ over the reaction mixture. H₂O (5 mL) was added and the reaction mixture was neutralized (pH 7) with 2N HCl. The resulting precipitate was collected by filtration
10 and dried by concentration in vacuo with acetonitrile to provide the amino acid as an off-white solid (1.07 g, 79%).

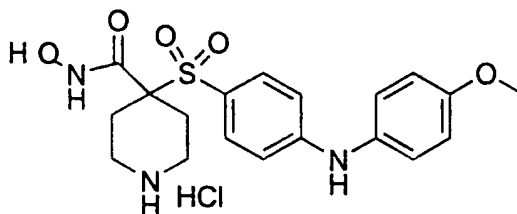
Part C: To a suspension of the amino acid of part B (1.07 g, 2.06 mmol) in N,N-dimethylformamide
15 (10 mL) was added 1-hydroxybenzotriazole (0.333 g, 2.47 mmol), N-methylmorpholine (0.679 mL, 6.18 mmol), O-(tetrahydropuranyl) hydroxylamine (0.362 g, 3.09 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.553 g, 2.88 mmol).
20 The resulting mixture was stirred at ambient temperature for 19 hours, then concentrated in vacuo. The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried
25 over Na₂SO₄. Chromatography (on silica, methanol/dichloromethane) provided the protected hydroxamate as a white solid (1.03 g, 81%).

Part D: To a solution of the protected hydroxamate of part C (1.03 g, 1.66 mmol) in dioxane
30 (3.0 mL) and methanol (1.0 mL) was added a solution of 4N HCl in dioxane (3.0 mL, 12.00 mmol). After stirring at ambient temperature for 1.5 hours, diethyl ether was added and the resulting precipitate

-600-

was collected by filtration to provide the title compound as a pale pink solid (0.970 g, 96%). MS MH^+ calculated for $C_{25}H_{25}O_5N_3SF_3$: 536, found 536.

- 5 Example 392: Preparation of N-hydroxy-4-[[4-[(4-methoxyphenyl)amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



10

Part A: To the ester of part C, Example 91 (1.00 g, 2.17 mmol) was added Cs_2CO_3 (0.990 g, 3.04 mmol), BINAP (0.061 g, 0.098 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.060 g, 0.07 mmol), p-anisidine (0.320 g, 2.60 mmol) and toluene (4 mL). The resulting mixture was heated to one hundred degrees Celsius for 22 hours. After cooling to ambient temperature, diethyl ether was added and the mixture was filtered through a pad of Celite®, washing with ethyl acetate. The filtrate was concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexane) provided the aniline as an orange foam (0.810 g, 74%).

Part B: To a solution of the aniline of part A (0.780 g, 1.55 mmol) in tetrahydrofuran (4.0 mL) was added potassium trimethylsilanolate (0.238 g, 1.86 mmol). The resulting mixture was stirred at ambient temperature for 17 hours, and then additional potassium trimethylsilanolate (0.020 g, 0.1955mmol)

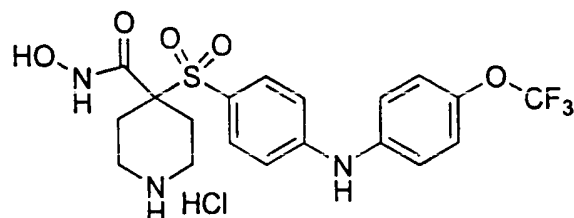
-601-

was added. After stirring at ambient temperature for 24 hours additional potassium trimethylsilanolate (0.040 g, 0.310 mmol) was added. After stirring at ambient temperature for 26 hours, the solvent was removed by blowing N₂ over the mixture. To a suspension of the residue in dichloromethane (10 mL) was added N-methylmorpholine (0.511 mL, 4.65 mmol), O-(tetrahydropuranyl) hydroxylamine (0.218 g, 1.86 mmol), followed by PyBroP® (1.08 g, 2.33 mmol). The resulting mixture was stirred at ambient temperature for 2 days and then concentrated *in vacuo*. The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an off-white solid (0.600 g, 66%).

Part C: To a solution of the protected hydroxamate of part B (0.580 g, 0.984 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (2.5 mL, 10.0 mmol). The resulting mixture was stirred at ambient temperature for 1 hour, then diethyl ether (10 mL) was added. The solids were collected by filtration to give the title compound as a white solid (0.437 g, 100%). MS MH⁺ calculated for C₁₉H₂₄O₅N₃S: 406, found 406.

Example 393: Preparation of N-hydroxy-4-[[4-[[4-(trifluoromethoxy)phenyl]amino]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the ester of part C, Example 91 (3.27 g, 7.09 mmol) was added Cs_2CO_3 (3.23 g, 9.92 mmol), BINAP (0.066 g, 0.107 mmol),
5 tris(dibenzylideneacetone)-dipalladium (0) (0.065 g, 0.071 mmol), 4-trifluoro-methoxyaniline (1.15 mL, 8.51 mmol) and toluene (14 mL). The resulting mixture was heated to one hundred degrees Celsius for
10 22 hours. After cooling to ambient temperature, the mixture was filtered through a pad of Celite®, washing with ethyl acetate, and the filtrate was concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexane) provided the aniline as a tan
15 solid (3.59 g, 91%).

Part B: To a solution of the aniline of part A (1.03 g, 1.84 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.331 g, 2.58 mmol). The resulting mixture was stirred at ambient
20 temperature for 24 hours, and then additional potassium trimethylsilanolate (0.118 g, 0.092 mmol) was added. After stirring at ambient temperature for 24 hours, the solvent was removed by blowing N_2 over the mixture. H_2O was added and the reaction mixture
25 was acidified (pH 3) with 1N HCl. The aqueous reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4 . Concentration

-603-

in vacuo provided the acid as a tan solid (1.01 g, 100%).

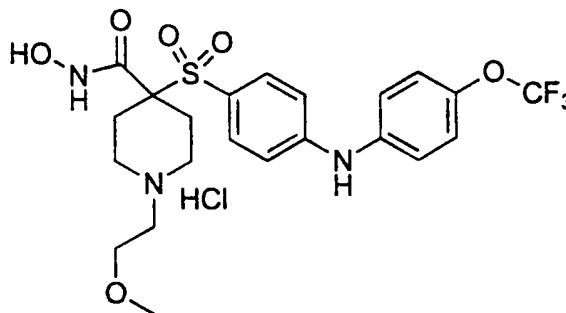
Part C: To a suspension of the acid of part B (1.00 g, 1.84 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.298 g, 2.21 mmol), N-methylmorpholine (0.607 mL, 5.52 mmol), O-(tetrahydropuranyl) hydroxylamine (0.323 g, 2.76 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.494 g, 2.58 mmol). The resulting mixture was stirred at ambient temperature for 17 hours then concentrated in vacuo. The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a white solid (0.960 g, 81%).

Part D: To a solution of the protected hydroxamate of part C (0.960 g, 1.49 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (4.0 mL, 16.0 mmol). The resulting mixture was stirred at ambient temperature for 2.5 hours. The solvent was then removed by blowing N₂ over the reaction mixture. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to give the title compound as a pale pink solid (0.716 g, 100%). MS MH⁺ calculated for C₁₉H₂₁O₅N₃SF₃: 460, found 460.

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Example 394: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[4-(trifluoromethoxy)phenyl]amino]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

5



Part A: To a solution of the aniline of
10 part A, Example 392 (2.55 g, 4.57 mmol) in dioxane
(9.0 mL) and methanol (3.0 mL) was added a solution
of 4N HCl in dioxane (10 mL, 40 mmol). After
stirring at ambient temperature for 2 hours, the
reaction mixture was concentrated *in vacuo* to provide
15 the amine as a tan solid (2.36 g, >100%).

Part B: To a suspension of the amine of part A
(1.50 g, 3.03 mmol) in acetonitrile (12 mL) was added
K₂CO₃ (1.26 g, 9.09 mmol) and 2-bromoethyl methyl
ether (0.313 mL, 3.33 mmol). After stirring at
20 reflux for 23 hours, Cs₂CO₃ (2.96 g, 9.09 mmol) was
added. After 6 hours at reflux, the reaction mixture
was filtered through a pad of Celite®, washing with
dichloromethane. The filtrate was concentrated *in*
vacuo. Chromatography (on silica, methanol/
25 dichloromethane) provided the methoxy ethyl amine as
a tan solid (1.13 g, 72%).

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Part C: To a solution of the methoxy ethyl amine of part B (1.13 g, 2.19 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilanolate (0.561 g, 4.38 mmol). The
5 resulting mixture was stirred at ambient temperature for 18 hours, and then additional potassium trimethylsilanolate (0.140 g, 1.09 mmol) was added. After stirring at ambient temperature for 5 hours, the solvent was removed by blowing N₂ over the
10 mixture. Water (8 mL) was added and the reaction mixture was neutralized (pH 7) with 1N HCl. The solids were collected by filtration and dried by concentration in vacuo with acetonitrile to provide the amino acid as an off-white solid (0.900 g, 82%).

15 Part D: To a suspension of the amino acid of part C (0.900 g, 1.79 mmol) in N,N-dimethylformamide (8.0 mL) was added 1-hydroxybenzotriazole (0.290 g, 2.15 mmol), N-methylmorpholine (0.590 mL, 5.37 mmol), O-(tetrahydropuranyl) hydroxylamine (0.315 g, 2.69
20 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.480 g, 2.51 mmol). The resulting mixture was stirred at ambient temperature for 16 hours then concentrated in vacuo. The residue was partitioned between H₂O and ethyl
25 acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, methanol/dichloromethane) provided the protected hydroxamate as an off-white solid (0.870 g, 81%).

30 Part E: To a solution of the protected hydroxamate of part D (0.870 g, 1.45 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (10 mL, 40.0 mmol). The resulting

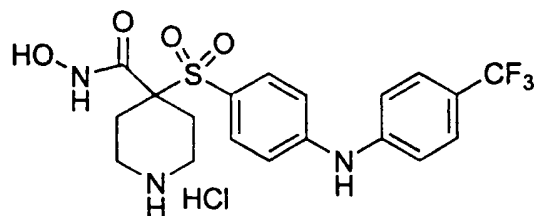
-606-

mixture was stirred at ambient temperature for 2.0 hours. The reaction mixture was concentrated in vacuo and then treated again with 4N HCl (3 mL) for 30 minutes. The solvent was then removed by blowing
5 N₂ over the reaction mixture. Diethyl ether (30 mL) was added, and the precipitate was collected by filtration to give the title compound as a pale pink solid (0.771 g, 96%). MS MH⁺ calculated for C₂₂H₂₇O₆N₃SF₃: 518, found 518.

10

Example 395: Preparation of N-hydroxy-4-[[4-[[4-(trifluoromethyl)phenyl]amino]phenyl]-sulfonyl]-4-piperidinecarboxamide,
monohydrochloride

15



Part A: To a solution of the ester of part C, Example 91 (3.16 g, 6.85 mmol) was added Cs₂CO₃ (3.13
20 g, 9.59 mmol), BINAP (0.064 g, 0.103 mmol), tris(dibenzylideneacetone)-dipalladium (0) (0.063 g, 0.069 mmol), α,α,α-trifluoro-methylaniline (1.03 mL, 8.22 mmol) and toluene (14 mL). The resulting mixture was heated to one hundred degrees Celsius for
25 17 hours. After cooling to ambient temperature, the mixture was filtered through a pad of Celite®, washing with dichloromethane, and the filtrate was concentrated in vacuo. Chromatography (on silica,

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ethyl acetate/hexane) provided the aniline as a pale orange foam (3.08 g, 83%).

Part B: To a solution of the aniline of part A (1.00 g, 1.84 mmol) in tetrahydrofuran (10 mL) was
5 added potassium trimethylsilanolate (0.473 g, 3.69 mmol). The resulting mixture was stirred at ambient temperature for 25 hours then the solvent was removed by blowing N₂ over the mixture. Water was added, and the reaction mixture was acidified (pH 3) with 1N
10 HCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na₂SO₄. Concentration *in vacuo* provided the acid as an orange foam (1.00 g, >100%).

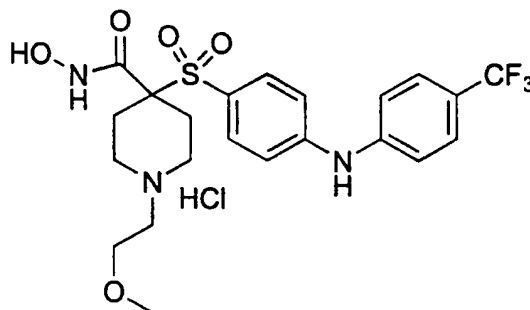
15 Part C: To a suspension of the acid of part B (0.972 g, 1.84 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.298 g, 2.21 mmol), N-methylmorpholine (0.607 mL, 5.52 mmol), O-(tetrahydropuranyl) hydroxylamine (0.323 g, 2.76
20 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.494 g, 2.58 mmol). The resulting mixture was stirred at ambient temperature for 18 hours, then concentrated *in vacuo*. The residue was partitioned between H₂O and ethyl
25 acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a white solid (0.970 g, 84%).

30 Part D: To a solution of the protected hydroxamate of part C (0.950 g, 1.51 mmol) in dioxane (3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (4.0 mL, 16.0 mmol). The resulting

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mixture was stirred at ambient temperature for 1.5 hours. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to give the title compound as a white solid (0.630 g, 87%). MS
5 MH^+ calculated for $C_{19}H_{21}O_4N_3SF_3$: 444, found 444.

Example 396: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[4-(trifluoromethyl)phenyl]amino]phenyl]sulfonyl]-4-piperidinecarboxamide,
10 monohydrochloride



15

Part A: To a solution of the aniline of part A, Example 395 (2.07 g, 3.82 mmol) in dioxane (9.0 mL) and methanol (3.0 mL) was added a solution of 4N HCl in dioxane (10 mL, 40 mmol). After stirring at
20 ambient temperature for 2 hours, the reaction mixture was concentrated in vacuo to provide the amine as a yellow solid (1.89 g, >100%).

Part B: To a suspension of the amine of part A (1.83 g, 3.82 mmol) in acetonitrile (20 mL) was added
25 K_2CO_3 (1.58 g, 11.46 mmol) and 2-bromoethyl methyl ether (0.395 mL, 4.20 mmol). After stirring at reflux for 18 hours, the reaction mixture was

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filtered through a pad of Celite®, washing with dichloromethane and the filtrate was concentrated in vacuo. Chromatography (on silica, methanol/dichloromethane) provided the methoxy ethyl
5 amine as an off-white solid (1.58 g, 83%).

Part C: To a solution of the methoxy ethyl amine of part B (1.58 g, 3.15 mmol) in tetrahydrofuran (30 mL) was added potassium trimethylsilanolate (0.810 g, 6.31 mmol). The
10 resulting mixture was stirred at ambient temperature for 3 days, and then the solvent was removed by blowing N₂ over the mixture. Water (10 mL) was added and the reaction mixture was neutralized (pH 7) with 1N HCl. The solids were collected by filtration and
15 dried by concentration in vacuo with acetonitrile to provide the amino acid as a pink solid (1.32 g, 86%).

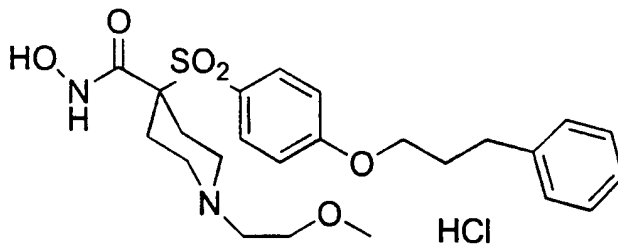
Part D: To a suspension of the amino acid of part C (1.32 g, 2.71 mmol) in N,N-dimethylformamide (12 mL) was added 1-hydroxybenzotriazole (0.439 g,
20 3.25 mmol), N-methylmorpholine (0.894 mL, 8.13 mmol), O-(tetrahydropuranyl) hydroxylamine (0.476 g, 4.07 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.727 g, 3.79 mmol). The resulting mixture was stirred at ambient
25 temperature for 20 hours, then concentrated in vacuo. The residue was partitioned between H₂O and ethyl acetate. The combined organic layers were washed with H₂O, saturated NaHCO₃, saturated NaCl and dried over Na₂SO₄. Chromatography (on silica,
30 methanol/ethyl acetate) provided the protected hydroxamate as an off-white solid (1.39 g, 88%).

Part E: To a solution of the protected hydroxamate of part D (1.40 g, 2.39 mmol) in dioxane

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(3 mL) and methanol (1 mL) was added a solution of 4N HCl in dioxane (5.98 mL, 23.9 mmol). The resulting mixture was stirred at ambient temperature for 2.5 hours. The reaction mixture was concentrated almost to dryness, by blowing N₂ over the reaction mixture. Diethyl ether (25 mL) was added and the precipitate was collected by filtration. The resulting solid was dissolved in methanol (1 mL) and treated with 4N HCl in dioxane (1.5 mL). After stirring at ambient temperature for 1.5 hours, the reaction mixture was slowly added to diethyl ether (50 mL). The resulting precipitate was collected by filtration to give the title compound as an off-white solid (1.08 g, 84%). MS MH⁺ calculated for C₂₂H₂₇O₅N₃SF₃: 502, found 502.

Example 397: Preparation of ethyl 1-(2-methoxyethyl)-3-phenylpropoxy)phenyl)sulfonyl]-4-piperidinecarboxylate



20

Part A: A mixture of the methoxyethyl amine, ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.5 g, 4.0 mmol), 3-phenyl-1-propanol (2.2 mL, 16 mmol), and K₂CO₃ (2.2 g, 16 mmol) in DMAC (6 mL) was heated at 125 degrees Celsius for 1 day and at 135 degrees Celsius for 3 days. After the mixture was

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concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo to give a crude oil. The oil was purified by flash chromatography (20:80 hexane/ethyl acetate) to afford the ether as a brown oil (1.35 g, 67%).

Part B: A mixture of the ether of part A (1.3 g, 2.7 mmol) and a 50% NaOH aqueous solution (2.1 g, 27 mmol) in THF (23 mL), EtOH (23 mL), and H₂O (12 mL) was heated at 60 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated in vacuo and triturated with diethyl ether to give a solid. The solid was dissolved in water, cooled with an ice bath, acidified with concentrated hydrochloric acid. The precipitate was isolated by filtration, washed with cold water, and dried at ambient temperature in a vacuum oven for 3 days to afford the crude acid.

A mixture of the above crude acid (1.1 g), N-hydroxybenzotriazole (0.36 g, 2.7 mmol), 4-methylmorpholine (0.74 mL, 6.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.39 g, 3.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.60 g, 3.1 mmol) in DMF (11 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18 hours. The mixture was concentrated in vacuo, and dissolved into a solution of saturated NaHCO₃ (90 mL), ethyl acetate (25 mL), and a few drops of 2N NaOH. The aqueous layer was extracted with additional ethyl acetate. The combined ethyl acetate layers were washed with saturated NaHCO₃ solution, water, and brine. After

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drying over magnesium sulfate, the filtrate was concentrated *in vacuo* to give a dark yellow oil. The oil was purified by flash chromatography (40:60 acetonitrile/toluene) to afford the protected

5 hydroxamate as a yellow oil (0.32 g, 25%): MS MH⁺ calcd. for C₂₉H₄₀N₂O₇S 561, found 561.

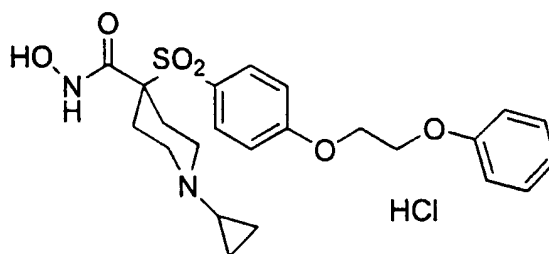
Part C: To a solution of the protected hydroxamate of part 2B (0.28 g, 0.50 mmol) in methanol (4.0 mL) was added acetyl chloride (0.11 mL,

10 1.5 mmol) and the solution was stirred at ambient temperature under a nitrogen atmosphere for 2.5 hours. The solution was diluted with diethyl ether and concentrated. The solid was triturated with diethyl ether and dried at 40 degrees Celsius in a

15 vacuum oven to give the title compound as an off white solid (0.15 g, 20%): MS MH⁺ calcd. for C₂₄H₃₂N₂O₆S 477, found 477.

Example 398: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-(2-phenoxyethoxy)phenyl]sulfonyl]-4-piperidinecarboxamide,

20 monohydrochloride



25 Part A: To a solution of the product of Example 9, part E (14.36 g, 40 mmol) in methanol (50 mL) was added acetic acid (24.5 g, 400 mmol), a portion (about 2 g) of 4-Angstrom molecular sieves,

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(1-ethoxycyclopropyl)-oxytrimethyl silane (25.8 mL, 148 mmol) and sodium cyanoborohydride (7.05 g, 112 mmol). The solution was heated at reflux for 8 hours. The precipitated solids were removed by
5 filtration and the filtrate was concentrated in vacuo. The residue was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. The solid was
10 filtered, washed with H₂O/diethyl ether to give the desired cyclopropyl amine {ethyl-4-[(4-fluorophenyl-sulfonyl)]-1-cyclopropyl-4-piperidinecarboxylate} as a white solid (11.83 g, 81.5%). MS MH⁺ calculated for C₁₇H₂₂NO₄SF: 356, found : 356.

15 Part B: A solution of the cyclopropyl amine of Part A (2.0 g, 5.6 mmol), ethylene glycol phenyl ether (2.8 mL, 23 mmol), and cesium carbonate (7.3 g, 23 mmol) in DMAC (10 mL) was heat at 125-135 degrees Celsius for 18 hours under an atmosphere of nitrogen.
20 The mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water and brine, dried over magnesium sulfate, concentrated in vacuo, dissolved in diethyl ether, precipitated as
25 the hydrochloride salt, and dried at 40 degrees Celsius in a vacuum oven. The solid was dissolved into a mixture of water, acetonitrile, and ethanol and then the pH was adjusted to 12 with 1N NaOH solution. The mixture was concentrated in vacuo to
30 remove ethanol and acetonitrile. The solid was isolated by filtration, washed with water, and dried at 50 degrees Celsius in a vacuum oven to afford the ether as a white solid (1.8 g, 68%): MS+ calcd. for

-614-

$C_{25}H_{31}NO_6S$ 474, found 474. Anal. calcd. for $C_{25}H_{31}NO_6S$: C, 63.40; H, 6.60; N, 2.96; S, 6.77. Found: C, 63.35; H, 6.59; N, 2.99; S, 6.61.

Part C: A mixture of the ether of part B
5 (1.8 g, 3.7 mmol) and a 50% NaOH aqueous solution (3.0 g, 37 mmol) in THF (32 mL), EtOH (32 mL), and H_2O (16 mL) was heated at 60 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated in vacuo and triturated with diethyl
10 ether to give a solid. The tan solid was dissolved into a mixture of water, ethanol, and THF, precipitated by adjusting the pH to 3 with concentrated hydrochloric acid, concentrated in vacuo, triturated with water, and dried at 50 degrees
15 Celsius in a vacuum oven to give a crude white solid acid (2.3 g).

A mixture of the crude white solid acid (2.3 g), N-hydroxybenzotriazole (1.9 g, 14 mmol), 4-methylmorpholine (1.6 mL, 14 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.1 g, 9.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.7 g, 14 mmol) in DMF (90 mL) was stirred at ambient temperature under a nitrogen atmosphere for 2 days. The mixture was concentrated
25 in vacuo, diluted with water, and extracted with ethyl acetate. The organic layer was washed with 1N NaOH solution, water, and brine, dried over magnesium sulfate, concentrated in vacuo, and purification by flash chromatography (20:80 to 40:60 ethyl
30 acetate/toluene) to afford the protected hydroxamate as a white solid: (0.43 g, 21%): MS MH^+ calcd. for $C_{28}H_{36}N_2O_7S$ 545, found 545. Anal. calcd. for

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$C_{28}H_{36}N_2O_7S$: C, 61.74; H, 6.66; N, 5.14; S, 5.89.

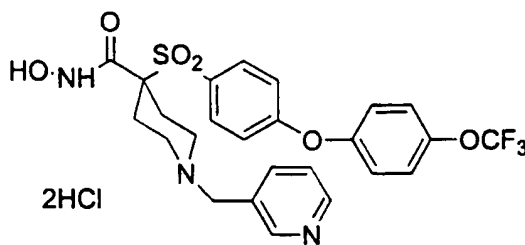
Found: C, 61.72; H, 6.75; N, 5.06; S, 5.91.

Additional compound was isolated by acidifying the aqueous layer to pH of 3, collecting
5 the solid by filtration, and drying to give a white solid (0.80 g).

Part D: To an ambient temperature solution of acetyl chloride (0.31 mL, 4.4 mmol) in methanol (11 mL) under a nitrogen atmosphere was added the
10 protected hydroxamate of part C (0.80 g, 1.5 mmol). After stirring for 2.5 hours, the precipitate was collected by filtration, washed with diethyl ether, and dried at 45 degrees Celsius in a vacuum oven to afford the title compound as a white solid (0.58 g,
15 79%): MS MH^+ calcd. for $C_{23}H_{28}N_2O_6S$ 461, found 461. Anal. calcd. for $C_{23}H_{28}N_2O_6S \cdot 1.5HCl$: C, 53.62; H, 5.77; N, 5.44; S, 6.22. Found: C, 53.47; H, 5.79; N, 5.41; S, 6.16.

20 Example 399: Preparation of hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride

25



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Part A: A solution of the amine hydrochloride salt of the product of Example 410 (2.4 g, 4.6 mmol), 3-picolyl chloride (1.5 g, 8.8 mmol), and potassium carbonate (4.3 g, 31 mmol) in DMF (12) was heated at 50 degrees Celsius for 1 day under an atmosphere of nitrogen. The mixture was concentrated in vacuo, dissolved into water, and extracted with ethyl acetate. The organic layers were washed with water and brine, dried over magnesium sulfate, concentrated in vacuo. The residue was purified by flash chromatography (50:50 ethyl acetate/hexane) to afford the 3-picolyl amine as an amber oil (1.6 g, 60%): MS MH⁺ calcd. for C₂₇H₂₇N₂O₆SF₃ 565, found 565. Anal. calcd. for C₂₇H₂₇N₂O₆SF₃: C, 57.44; H, 4.82; N, 4.96; S, 5.68. Found: C, 57.49; H, 5.10; N, 4.69; S, 5.67

Part B: A mixture of the 3-picolyl amine of part 4A (1.5 g, 2.6 mmol) and a 50% NaOH aqueous solution (2.1 g, 26 mmol) in THF (22 mL), EtOH (22 mL), and H₂O (11 mL) was heated at 65 degrees Celsius under a nitrogen atmosphere for 24 hours. The material was concentrated in vacuo and triturated with diethyl ether to give a solid. The tan solid was dissolved into water and the pH was adjusted to 1 with concentrated hydrochloric acid. The mixture was concentrated in vacuo, and dried in a 45 degrees Celsius vacuum oven to afford the crude white solid acid (2.5 g): MS MH⁺ calcd. for C₂₅H₂₃N₂O₆SF₃ 537, found 537.

Part C: A mixture of the crude white acid of part B (2.5 g), N-hydroxybenzotriazole (1.0 g, 7.7 mmol), 4-methylmorpholine (0.64 mL, 7.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.60 g, 5.1

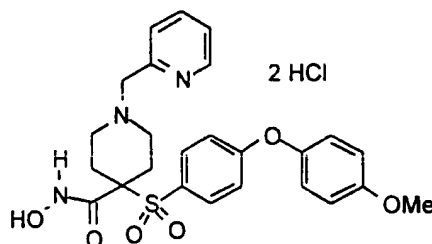
-617-

mmol), and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 7.7 mmol) in DMF (40 mL) was stirred at ambient temperature under a nitrogen atmosphere for 5 days. The mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over magnesium sulfate, concentrated in vacuo, and purified by flash chromatography (5:95 methanol/chloroform) to afford the protected hydroxamate as a white foam (1.1 g, 66%): MS MH+ calcd. for $C_{30}H_{32}N_3O_7SF_3$ 636, found 636.

Part D: An ambient temperature solution of the protected hydroxamate of part C (1.0 g, 1.6 mmol) and acetyl chloride (0.34 mL, 4.7 mmol) in methanol (11 mL) under a nitrogen atmosphere was stirring for 2.5 hours, and then poured into diethyl ether. The solid was isolated by filtration and dried at 46 degrees Celsius in a vacuum oven to afford the title compound as a white solid (0.85 g, 87%): Anal. calcd. for $C_{25}H_{24}N_3O_6SF_3 \cdot 2.2HCl$: C, 47.53; H, 4.18; N, 6.65; S, 5.08. Found: C, 47.27; H, 4.34; N, 6.60; S, 5.29. MS MH+ calcd. for $C_{25}H_{24}N_3O_6SF_3$ 552, found 552.

Example 400: Preparation of N-Hydroxy-4-[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-pyridinylmethyl)-4-piperidine-carboxamide, dihydrochloride

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Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-4-piperidinecarboxylate hydrochloride (2.02 g, 5.76 mmol) was combined with powdered potassium carbonate (2.48 g, 18 mmol) and N,N-dimethylformamide (12 mL). 2-Picolyl hydrochloride (1.0 g, 6.1 mmol) was added, and the mixture was stirred for twenty-four hours at forty degrees Celsius. The reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (3 X 50mL). The combined organic layers were dried over magnesium sulfate, concentrated, and subjected to chromatography (ethyl acetate) affording the desired pyridine ester as an oil (2.30 g, quantitative).

Part B: The pyridine ethyl ester from Part A (2.30 g, 5.76 mmol) was combined with powdered potassium carbonate (1.29 g, 9 mmol), 4-methoxyphenol (1.12 g, 9.0 mmol), and N,N-dimethylformamide (3 mL), and the mixture was heated at seventy five to eighty degrees C for twenty-four hours. Additional 4-methoxyphenol (300 mg) and potassium carbonate (350 mg) were added, and the mixture was stirred an additional three hours at ninety degrees Celsius. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were dried using magnesium

-619-

sulfate, concentrated, and chromatographed, affording the desired ester as an oil (2.85 g, quantitative).

Part C: The ester of part B (2.85 g) was combined with ethanol (18 mL), water (6 mL), and
5 potassium hydroxide (2.24 g, 40 mmol). The mixture was brought to reflux and heated for four and one-half hours. It was cooled to zero degrees Celsius and acidified using concentrated aqueous hydrogen chloride. The solvent was removed, and the resulting
10 solids were dried by azeotroping with acetonitrile. Vacuum was applied until constant weight was achieved.

The crude acid hydrochloride was stirred with N-methylmorpholine (1 mL), 1-
15 hydroxybenzotriazole (0.945 g, 7 mmol), O-tetrahydropyranyl hydroxylamine (0.82 g, 7 mmol), and N,N-dimethylformamide (21 mL). After ten minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.34 g, 7 mmol) was added, and the
20 mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (200 mL, then 50 mL). The combined organic layers were dried over magnesium sulfate,
25 concentrated, and chromatographed (9:1 ethyl acetate:hexane) to afford the desired O-tetrahydropyranyl-protected hydroxamate as a yellow oil (2.82 g, 88%).

Part D: The O-tetrahydropyranyl-protected hydroxamate of part C (2.82 g, 5 mmol) was diluted
30 with methanol (20 mL). Acetyl chloride (2.1 mL, 30 mmol) was added over two minutes. The reaction was stirred for 4 hours at ambient temperature, then concentrated to afford 2.59 g of crude

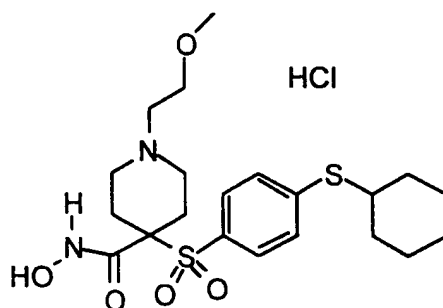
- 620 -

dihydrochloridesalt, which was recrystallized from ethanol/water, affording 525 mg (18%) of the title hydroxamate in the first crop. MS (EI) MH^+ calculated for $C_{25}H_{27}N_3O_6S$: 498, found 498.

5

Example 401: Preparation of N-Hydroxy-4-[4-(4-cyclohexylthio)phenyl]sulfonyl]-1-(2-methoxyethyl)-4-piperidine-carboxamide, hydrochloride

10



Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (5.5 g, 14 mmol) was combined with powdered potassium carbonate (2.76 g, 20 mmol), N, N-dimethylformamide (7 mL), and cyclohexyl mercaptan (2.4 mL, 20 mmol) and was stirred at ambient temperature for two days. The temperature was raised to forty-five to fifty degrees Celsius and stirring was continued another 24 hours. Additional quantities of potassium carbonate (1.0 g) and cyclohexyl mercaptan (1.0 mL) were introduced and the reaction was heated sixteen additional hours. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (100 mL, then 25 mL). The combined organic layers were dried, concentrated,

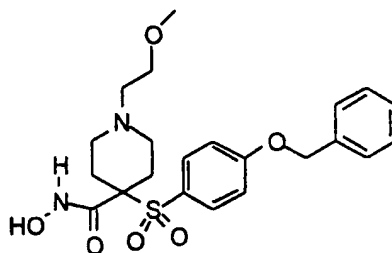
-621-

and chromatographed (ethyl acetate) affording the desired sulfide as a yellow oil (3.59 mL, 53%).

Part B: The sulfide from Part A (3.59 gm, 7.4 mmol) was converted to tetrahydropyranyl-protected hydroxamate by saponification followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 2.16 g (54%) of the desired tetrahydropyranyl-protected hydroxamate as an oil.

Part C: The tetrahydropyranyl-protected hydroxamate from part B (2.16 g, 4 mmol) was diluted with methanol (16 mL). Acetyl chloride (1.1 mL, 16 mmol) was added over one minute. The reaction was stirred for four hours, then concentrated and azeotroped with acetonitrile to afford 1.11 g of crude product, which was recrystallized from absolute ethanol to afford in the first crop 804 mg of the title compound (41%). MS (EI) MH^+ calculated for $C_{21}H_{32}N_2O_5S_2$: 457, found 457.

Example 402: Preparation of N-Hydroxyl-1-(2-methoxyethyl)-4-[[(phenylmethoxy) phenyl]-sulfonyl]-4-piperidinecarboxamide



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Part A: Ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.58 g, 4.5 mmol) was combined with powdered potassium carbonate (2.42 g, 18 mmol), N,N-dimethylacetamide (5 mL), and benzyl alcohol (1.94 mL, 18 mmol) and was stirred at one hundred forty degrees Celsius for sixteen hours. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (125 mL, then 25 mL). The combined organic layers were dried, concentrated, and chromatographed (ethyl acetate) affording the desired ethyl ester as an oil (1.16 mL, 56%).

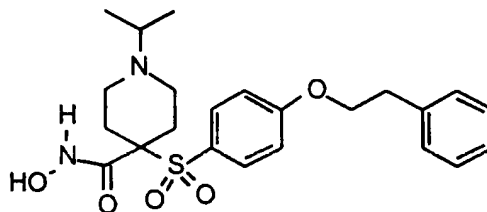
Part B : The ethyl ester from part A (1.16 gm, 2.5 mmol) was converted to the tetrahydropyranyl-protected hydroxamate by saponification followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 880 mg (80%) of the tetrahydropyranyl-protected hydroxamate as an oil.

Part C: The tetrahydropyranyl-protected hydroxamate from Part B (880 mg, 2.0 mmol) was diluted with methanol (8 mL). Acetyl chloride (0.68 mL, 10 mmol) was added over one minute. The reaction was stirred for three hours, then concentrated and azeotroped with acetonitrile to afford the crude product, which was converted to free base by adding enough saturated aqueous sodium bicarbonate (25 mL) to neutralize the hydrogen chloride, then extracting with ethyl acetate (100 mL, then 50 mL). The organic phase was dried with magnesium sulfate, concentrated, and chromatographed (9:1 dichloromethane:methanol, 1% ammonium hydroxide), affording the title hydroxamate

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as a glass, (327 mg, 36%). MS (EI) MH^+ calculated for $C_{22}H_{28}N_2O_6S$: 447, found 447.

Example 403: Preparation of N-hydroxyl-1-(1-methylethyl)-4-[[4-(2-phenylethoxy)-phenyl]sulfonyl]-4-piperidine
5 carboxamide



10

Part A: Ethyl-4-[[4-(4-fluorophenylsulfonyl)]]-1-(1-methylethyl)-4-piperidinecarboxylate (2.75 g, 7.7 mmol) was combined with powdered potassium carbonate (2.62 g, 19 mmol), N, N-dimethylformamide
15 (10 mL), and 2-phenylethanol (2. mL, 19 mmol) and was stirred at eighty-five degrees Celsius for twenty four hours. Additional potassium carbonate (1.3 g) and 2-phenylethanol were added, and the temperature was raised to one hundred-ten degrees Celsius for
20 forty-eight hours, then one hundred thirty-five degrees Celsius for four hours. The mixture was diluted with water (100 mL), and extracted with ethyl acetate (200 mL, then 25 mL). The combined organic layers were dried, concentrated, and chromatographed
25 (ethyl acetate) affording the desired ethyl ester as an oil (3.19 mL, 90%).

Part B: The ethyl ester from Part A (3.19 gm, 6.9 mmol) was converted to tetrahydropyranyl-protected hydroxamate by saponification followed by

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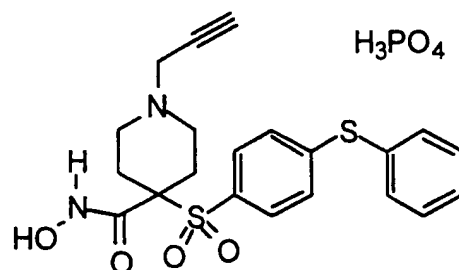
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling by the method of Example 401, part C, affording 2.27 g (64%) of the title compound as an oil.

5 Part C: The tetrahydropyranyl-protected hydroxamate from Part B (2.27 mg, 4.4 mmol) was diluted with methanol (16 mL). Acetyl chloride (0.68 mL, 10 mmol) was added over one minute. The reaction was stirred for three hours, then concentrated and
10 azeotroped with acetonitrile to afford the crude product, which was converted to free base by adding enough saturated sodium bicarbonate (25 mL) to neutralize the hydrogen chloride, then extracting with ethyl acetate (100, then 50 mL). The organic
15 phase was dried with magnesium sulfate, concentrated, and chromatographed (9:1 dichloromethane:methanol, 1% ammonium hydroxide), affording the desired hydroxamate as a glass, (819 mg, 42%). MS (EI) MH^+ calculated for $C_{23}H_{30}N_2O_5S$: 449, found 449.

20

Example 404: Preparation of N-hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, phosphoric acid salt

25

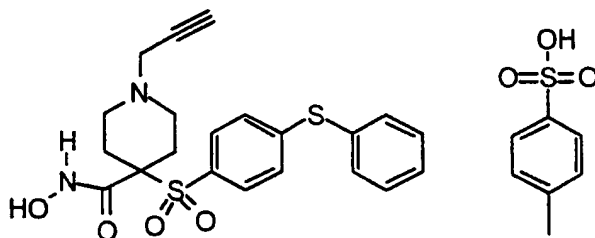


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N-Hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide (430 mg, 1.0
mmol) was dissolved in methanol (15 mL).

Concentrated phosphoric acid (67 μ L) was added, and
5 the solution was then concentrated *in vacuo*. The
residue was recrystallized from methanol, isolated by
filtration, and then recrystallized a second time
from methanol/methyl *t*-butyl ether affording the
title phosphate as a solid (215 mg, 41%). Analytical
10 calculation for $C_{21}H_{22}N_2O_4 \cdot H_3PO_4$: C, 47.72; H, 4.77; N,
5.30, found: C, 47.63; H, 5.04; N, 4.82.

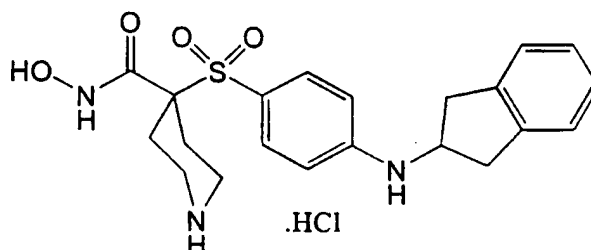
Example 405: Preparation of N-hydroxy-4-[(4-
phenylthiophenyl)sulfonyl]-1-
15 (2-propynyl)-4-piperidinecarboxamide,
p-toluenesulfonic acid salt



20 N-Hydroxy-4-[(4-phenylthiophenyl)sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide (516 mg, 1.0
mmol) was combined with *p*-toluenesulfonic acid,
monohydrate (200 mg, 1.05 mmol), and the mixture was
dissolved in methanol (3 mL). After four hours, the
25 resulting white precipitate was collected by
filtration affording 488 mg (81%) of the title
tosylate salt, which was characterized
spectroscopically.

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Example 406: Preparation of 4-[[4-[(2,3-dihydro-1H-inden-2-yl)amino]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,
5 monohydrochloride



Part A: A solution of the product of
10 Example 9, Part D (0.979 g, 2.36 mmol), 2-aminoindan
hydrochloride (1.00 g, 5.89 mmol), and cesium
carbonate (1.92 g, 5.89 mmol) in N,N-
dimethylformamide (8 mL) was heated to 95 degrees
Celsius for 22 hours. The reaction was then cooled,
15 diluted with ethyl acetate (50 mL), and washed with
three times with water and once with brine, then
dried over sodium sulfate. Concentration gave a
residue that was chromatographed on silica gel.
Elution with ethyl acetate/hexane (30/70) afforded
20 the desired 4-aminosulfone derivative (450 mg, 36%).
MS (EI) MH^+ calculated for $C_{28}H_{36}N_2O_6S$: 529, found 529.
HRMS M^+ calculated for $C_{28}H_{36}N_2O_6S$: 528.2294, found
528.2306.

Part B: To a solution of the ethyl ester
25 of part A (450 mg, 0.85 mmol) in ethanol (3 mL),
water (2 mL) and tetrahydrofuran (3 mL) was added
sodium hydroxide (340 mg, 8.5 mmol), and the solution
was heated to 60 degrees Celsius for 26 hours. The

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solution was cooled and then diluted with water (10 mL) followed by 10% aqueous hydrochloric acid (3 mL) to bring the pH to 2. The resulting solution was extracted with ethyl acetate. The organic extracts
5 were combined and washed with water and brine and dried over sodium sulfate to afford the desired carboxylic acid as a pale brown foam (376 mg, 88%). Analytical calculation for $C_{26}H_{32}N_2O_6S$: C, 62.38; H, 6.44; N, 5.60; S, 6.40. Found: C, 62.48; H, 6.69;
10 N, 5.42; S, 6.27.

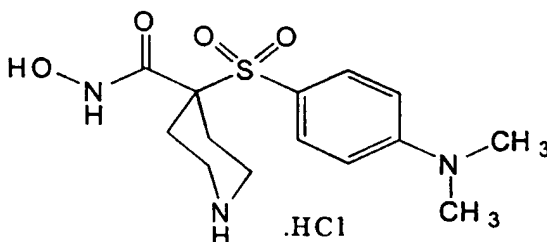
Part C: To a solution of the carboxylic acid of part B (305 mg, 0.609 mmol) in N,N-dimethylformamide (2 mL) was added 4-methylmorpholine (247 mg, 2.44 mmol), N-hydroxybenzotriazole (99 mg,
15 0.73 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (152 mg, 0.79 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (97 mg, 0.82 mmol). After stirring for 2 days at ambient temperature, the solution was
20 concentrated to an oil. Water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over sodium sulfate. Concentration gave a brown foam that was chromatographed on silica gel.
25 Elution with ethyl acetate/hexane (40/60) afforded the protected hydroxamate derivative as a colorless glass (0.38 g, 100%). MS MH^+ calculated for $C_{31}H_{41}N_3O_7S$: 600, found 600.

Part D: To a solution of the protected
30 hydroxamate of part C (350 mg, 0.584 mmol) in methanol (3 mL) and 1,4-dioxane (1.5 mL) was added 4 N HCl/1,4-dioxane (1.5 mL, 6 mmol), and the solution was stirred at ambient temperature for 3 hours.

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Concentration gave a residue that was triturated with diethyl ether to afford the title compound as a solid, which was filtered and dried for 40 hours at 51 degrees Celsius (249 mg, 94%). HRMS (ESI) MH^+ calculated for $C_{21}H_{25}N_3O_4S$: 416.1644, found 416.1647.

Example 407: Preparation of 4-[[4-(dimethylamino)-phenyl]sulfonyl]-N-hydroxy-4-piperidine-carboxamide,
monohydrochloride



Part A: A solution of the product of Example 9, Part D (0.979 g, 2.36 mmol), 2-aminoindan hydrochloride (1.00 g, 5.89 mmol), and cesium carbonate (1.92 g, 5.89 mmol) in N,N-dimethylformamide (8 mL) was heated to 95 degrees Celsius for 22 hours. The reaction was then cooled, diluted with ethyl acetate (50 mL), and washed with three times with water and once with brine, then dried over sodium sulfate. Concentration gave a residue that was chromatographed on silica gel. Elution with ethyl acetate/hexane (30/70) afforded the 4-N,N-dimethylaminosulfone derivative (590 mg, 57%) alongside the product of example 406. MS (EI) MH^+ calculated for $C_{21}H_{32}N_2O_6S$: 441, found 441. HRMS calculated for $C_{21}H_{32}N_2O_6S$: 440.1981, found 440.1978.

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Part B: To a solution of the ethyl ester of part A (580 mg, 1.3 mmol) in ethanol (4 mL), water (3 mL) and tetrahydrofuran (4 mL) was added sodium hydroxide (520 mg, 13 mmol), and the solution was
5 heated to 62 degrees Celsius for 5 hours. The solution was cooled and then diluted with water (5 mL) followed by 10% aqueous hydrochloric acid (5 mL) to acidify to pH=2. The resulting solution was extracted with ethyl acetate. The organic extracts
10 were combined and washed with water and brine and dried over sodium sulfate to afford the desired carboxylic acid as a pale brown foam (520 mg, 97%). MS MH⁺ calculated for C₁₉H₂₈N₂O₆S: 413, found 413.

Part C: To a solution of the carboxylic
15 acid of part B (500 mg, 1.21 mmol) in N,N-dimethylformamide (4 mL) was added 4-methylmorpholine (490 mg, 4.8 mmol), N-hydroxybenzotriazole (197 mg, 1.45 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (302 mg, 1.57 mmol)
20 followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (192 mg, 1.63 mmol). After stirring for 2 days at ambient temperature, the solution was concentrated to an oil. Water (25 mL) was added and the mixture was extracted with ethyl acetate. The
25 organic extracts were washed with water and brine and dried over sodium sulfate. Concentration gave a brown oil, which crystallized from a mixture of ethyl acetate, hexane and methylene chloride (1:1:2) to afford the protected hydroxamate derivative as a
30 colorless solid (506 mg, 82%). MS MH⁺ calculated for C₂₄H₃₇N₃O₇S: 512, found 512.

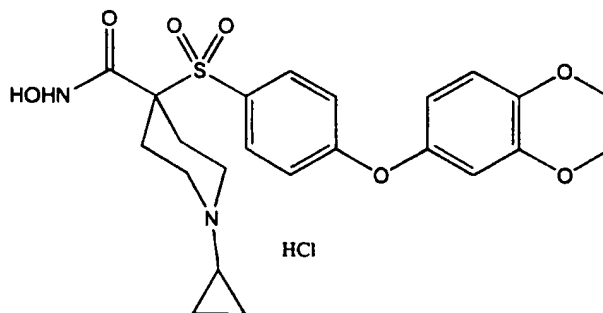
Part D: To a solution of the protected hydroxamate of part C (477 mg, 0.932 mmol) in

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methanol (3 mL) and 1,4-dioxane (3 mL) was added 4 N HCl/1,4-dioxane (2.3 mL, 9.3 mmol), and the solution was stirred at ambient temperature for 3 hours. Concentration gave a residue that was triturated with
5 diethyl ether to afford the title compound as a solid, which was filtered and dried for 40 hours at 51 degrees Celsius (372 mg, 100%). HRMS (ESI) MH^+ calculated for $C_{14}H_{21}N_3O_4S$: 328.1331, found 328.1343.

- 10 Example 408: Preparation of 1-cyclopropyl-4-[[4-
[(2,3-dihydro-1,4-benzodioxin-6-yl)oxy]
phenyl]-sulfonyl]-N-hydroxy-4-
piperidine-carboxamide,
monohydrochloride

15



- Part A: To a solution of the product of Example 398, Part A (1.36 g, 3.47 mol) in N,N-
20 dimethylformamide (8 mL) was added 6-hydroxybenzo-
1,4-dioxane (792 mg, 5.21 mmol) followed by cesium
carbonate (2.83 g, 8.69 mmol) and the solution was
heated at one hundred degrees Celsius for 20 hours.
The solution was partitioned between ethyl acetate
25 and H₂O. The aqueous layer was extracted with ethyl
acetate and the combined organic layers were washed
with H₂O and saturated NaCl and dried over Na₂SO₄.

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Filtration through a silica pad (ethyl acetate/hexane) provided the phenoxyphenyl compound as an orange oil (1.81 g, quantitative yield). MS(CI) MH^+ calculated for $C_{25}H_{29}NO_7S$: 488, found 488.

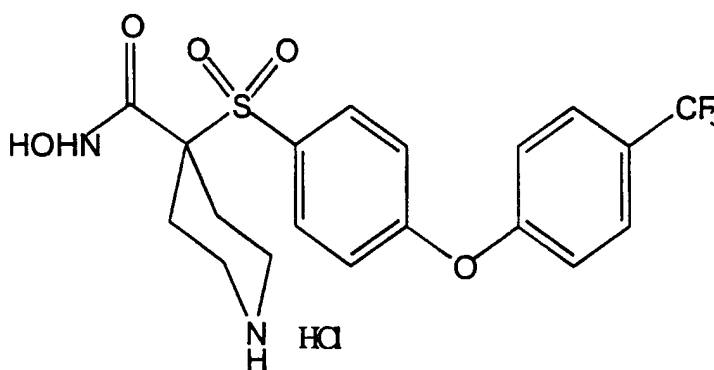
5 Part B: To a solution of the phenoxyphenol compound of part A (1.81 g, <3.47 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.39 g, 34.7 mmol) in H_2O (5 mL). The solution was heated to sixty degrees Celsius for
10 20 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH = 2 with 10% HCl. The resulting solid was collected by vacuum filtration to provide the acid as a yellow solid (1.23 g, 72%). MS(CI) MH^+ calculated for $C_{23}H_{25}NO_7S$:
15 460, found 460. HRMS calculated for $C_{23}H_{25}NO_7S$: 460.1430, found 460.1445.

Part C: To a suspension of the acid of part B (1.21 g, 2.46 mmol) in N,N-dimethylformamide (20 mL) was added N-hydroxybenzotriazole (399 mg, 2.95 mmol),
20 4-methylmorpholine (0.81 mL, 7.38 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (432 mg, 3.69 mmol). After stirring for one hour 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (660 mg, 3.44 mmol) was added and the
25 solution was stirred for 20 hours at ambient temperature. The solution was partitioned between ethyl acetate and H_2O and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4 .
30 Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a yellow oil (940 mg, 70 %). MS(CI) MH^+ calculated for $C_{28}H_{34}N_2O_2S$: 559, found 559.

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Part D: To a solution of the protected hydroxamate of part C (920 mg, 1.68 mmol) in 1,4-dioxane (15 mL) was added 4N HCl in 1,4-dioxane (10 mL). After stirring at ambient temperature for 2 hours the resulting precipitate was collected by vacuum filtration and washed with ethyl ether to provided the title compound as a white solid (510 mg, 60 %). MS(CI) MH^+ calculated for $C_{23}H_{26}N_2O_7S$: 475, found 475. HRMS calculated for $C_{23}H_{26}NO_7S$: 475.1539, found 475.1553. Analytical calculation for $C_{23}H_{26}N_2O_7S \cdot 1.15HCl \cdot 0.5H_2O$: C, 52.57; H, 5.40; N, 5.33; Cl, 7.76. Found: C, 52.62; H, 5.42; N, 5.79; Cl, 7.71.

Example 409: Preparation of N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



20

Part A: To a solution of the product of Example 9, Part D (1.5 g, 3.61 mmol) in N,N-dimethylformamide (10 mL) was added cesium carbonate (2.94 g, 9.03 mmol) and α,α,α -trifluoro-p-cresol (877 mg, 5.41 mmol). The solution was heated to ninety degrees Celsius for 20 hours. The solution was

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partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over Na₂SO₄. Filtration through a silica pad (ethyl acetate) provided the diaryl ether as a yellow oil (2.30 g, quantitative yield). MS(CI) MH⁺ calculated for C₂₆H₃₀NO₇SF₃: 558, found 558.

Part B: To a solution of the diaryl ether of part A (2.30 g, <3.61 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.44 g, 36.1 mmol) in H₂O (5 mL) and the solution was heated to sixty degrees Celsius for 18 hours. The solution was concentrated and the aqueous residue was acidified to pH = 2 with 10% HCl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the acid as a solid (2.11 g, quantitative yield). MS(CI) MH⁺ calculated for C₂₄H₂₆NO₇SF₃: 530, found 530.

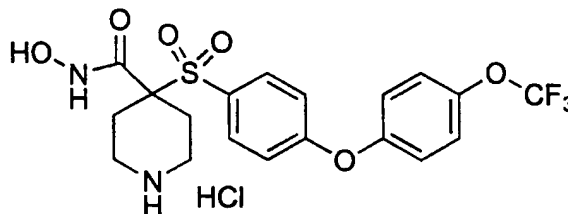
Part C: To a solution of the acid of part B (2.11 g, <3.61 mmol) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (586 mg, 4.33 mmol), 4-methylmorpholine (1.19 mL, 10.83 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for one hour, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (969 mg, 5.05 mmol) was added and the solution was stirred for 18 hours. The solution was partitioned between ethyl acetate and H₂O. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H₂O and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a clear, colorless oil (1.40

-634-

g, 62 %). MS(CI) MH^+ calculated for $C_{29}H_{35}N_2O_8SF_3$: 629, found 629.

Part D: To a solution of the protected hydroxamate of part C (1.40 g, 2.23 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in 1,4-dioxane (15 mL) and the solution was stirred for 2 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (747 mg, 70 %). HPLC purity: 97.5 %. MS(CI) MH^+ calculated for $C_{19}H_{19}N_2O_5SF_3$: 445, found 445. HRMS calculated for $C_{19}H_{19}N_2O_5SF_3$: 445.1045, found 445.1052. Analytical calculation for $C_{19}H_{19}N_2O_5SF_3 \cdot 0.5H_2O \cdot 1.0HCl$: C, 46.58; H, 4.32; N, 5.72; S, 6.55; Cl, 7.24. Found: C, 46.58; H, 3.82; N, 5.61; S, 6.96; Cl, 7.37.

Example 410: Preparation of N-hydroxy-4-[[4-[(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (1.5 g, 3.61 mmol) in N,N-dimethylformamide (10 mL) was added cesium carbonate (2.94 g, 9.03 mmol) and 4-(trifluoromethoxy)phenol (0.70 mL, 5.41 mmol). The solution was heated to ninety degrees Celsius for 20 hours. The solution

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was partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over Na₂SO₄. Filtration through a silica pad (ethyl acetate) provided the phenoxyphenol as a yellow oil (2.11 g, quantitative yield). MS(CI) MNa⁺ calculated for C₂₆H₃₀NO₈SF₃: 596, found 596.

Part B: To a solution of the phenoxyphenol of part A (2.11 g, <3.61 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.44 g, 36.1 mmol) in H₂O (5 mL), and the solution was heated to sixty degrees Celsius for 18 hours. The solution was concentrated and the aqueous residue was acidified to pH = 2 with 10% HCl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the acid as a solid (2.2 g, quantitative yield). MS(CI) MH⁺ calculated for C₂₄H₂₆NO₈SF₃: 546, found 546.

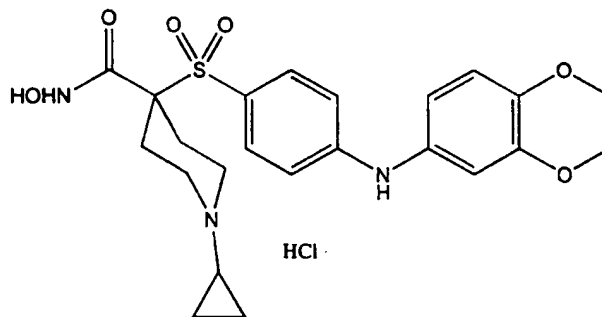
Part C: To a solution of the acid of part B (2.2 g) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (586 mg, 4.33 mmol), 4-methylmorpholine (1.19 mL, 10.83 mmol) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for thirty minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (969 mg, 5.05 mmol) was added and the solution was stirred for 96 hours. The solution was partitioned between ethyl acetate and H₂O. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H₂O and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the

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protected hydroxamate as a clear, colorless oil (1.26 g, 53 %).

Part D: To a solution of the protected hydroxamate of part C (1.26 g, 1.96 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in 1,4-dioxane (10 mL) and the solution was stirred for 2 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (455 mg, 47 %). HPLC purity: 98 %. MS(CI) MH^+ calculated for $C_{19}H_{19}N_2O_6SF_3$: 461, found 461. HRMS calculated for $C_{19}H_{19}N_2O_6SF_3$: 461.0994, found 461.0997. Analytical calculation for $C_{19}H_{19}N_2O_6SF_3 \cdot 1.0HCl$: C, 45.93; H, 4.06; N, 5.64; S, 6.45; Cl, 6.45. Found: C, 46.23; H, 4.07; N, 5.66; S, 6.59; Cl, 7.03.

Example 411: Preparation of 1-cyclopropyl-4-[[4-[(2,3-dihydro-1,4-benzodioxin-6-yl)amino]-phenyl]sulfonyl]-N-hydroxy-4-piperidine-carboxamide, monohydrochloride



Part A: To a solution of ester of part C, Example 91 (1.57 g, 3.40 mmol) in 1,4-dioxane (5 mL) was added 4M HCl in 1,4-dioxane (10 mL). After

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stirring for one hour the resulting precipitate was collected by vacuum filtration to provide the amine hydrochloride salt as a white solid (1.16 g, 86 %).

Part B: To a slurry of the amine

5 hydrochloride salt of part A (1.16 g, 2.91 mmol) in methanol (10 mL) was added acetic acid (1.68 mL, 29.1 mmol) followed by (1-ethoxycyclopropyl)-oxytrimethylsilane (3.51 mL, 17.5 mmol) and sodium cyanoborohydride (823 mg, 13.1 mmol). The solution
10 was heated to reflux for six hours. The solution was filtered and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H₂O, aqueous sodium hydroxide and saturated NaCl and dried over MgSO₄. Concentration in
15 vacuo provided the N-cyclopropyl compound as a white solid (1.03 g, 88 %).

Part C: To a solution of the N-cyclopropyl compound of part B (1.0 g, 2.49 mmol) in toluene (6 mL) was added cesium carbonate (1.14 g, 3.49 mmol),
20 tris(dibenzylideneacetone)dipalladium(0) (69 mg, 0.075 mmol) R-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (69 mg, 0.112 mmol) and 1,4-benzodioxane-6-amine (451 mg, 2.99 mmol) and the solution was heated to one hundred degrees Celsius for 19 hours.
25 The solution was diluted with ethyl ether and filtered through Super Cel[®]. The filtrate was concentrated and chromatography (on silica, ethyl acetate/hexane) provided the aniline compound as an orange oil (561 mg, 48 %). MS(CI) MH⁺ calculated for
30 C₂₄H₂₈N₂O₆S: 473, found 473.

Part D: To a solution of the aniline compound of part C (550 mg, 1.16 mmol) in tetrahydrofuran (10 mL) was added potassium

-638-

trimethylsilanolate (297 mg, 3.48 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated and the resulting residue was suspended in H₂O. The solid was
5 collected by vacuum filtration to provide the crude acid (282 mg).

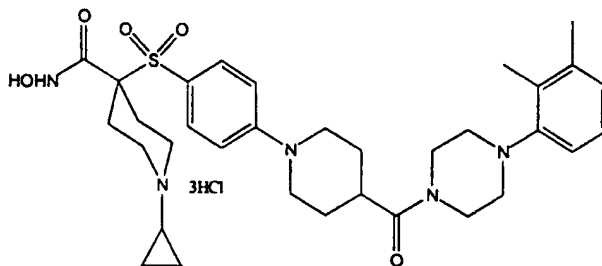
Part E: To a solution of the crude acid of part D (282 mg, 0.62 mmol) in N,N-dimethylformamide (10 mL) was added N-hydroxybenzotriazole (100 mg,
10 0.74 mmol), 4-methylmorpholine (0.20 mL, 1.86 mmol), and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (108 mg, 0.93 mmol). After stirring for 30 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (166 mg, 0.87 mmol) was added and the
15 solution was stirred for 72 hours. The solution was partitioned between ethyl acetate and H₂O and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H₂O and saturated NaCl and dried over Na₂SO₄. Chromatography
20 (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (150 mg, 43 %). MS(CI) MH⁺ calculated for C₂₈H₃₅N₃O₇S: 558, found 558.

Part F: To a solution of protected
25 hydroxamate of part E (133 mg, 0.24 mmol) in 1,4-dioxane (5 mL) was added 4N HCl in 1,4-dioxane (10 mL) and the solution was stirred for 1.5 hours. The solution was diluted with ethyl ether and the resulting precipitate was collected by vacuum
30 filtration to provide the title hydroxamate as a white solid (80 mg, 66 %). MS(CI) MH⁺ calculated for C₂₃H₂₇N₃O₆S: 474, found 474. HRMS calculated for C₂₃H₂₇N₃O₆S: 474.1699, found 474.1715. Analytical

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calculation for $C_{23}H_{27}N_3O_6S \cdot 1.5HCl \cdot 1.5H_2O$: C, 49.75; H, 5.72; N, 7.57; S, 5.77; Cl, 9.58. Found: C, 49.78; H, 5.52; N, 8.05; S, 9.16; Cl, 5.76.

- 5 Example 412: Preparation of 1-cyclopropyl-4-[[4-[4-
[[4-(2,3-dimethylphenyl)-1-
piperazinyl]-carbonyl]-1-
piperidinyl]phenyl]sulfonyl]-
N-hydroxy-4-piperidine-carboxamide,
10 trihydrochloride



- 15 Part A: To a solution of the isonipecotic acid (10.5 g, 81.3 mmol) in H_2O (325 mL) was added sodium carbonate (8.37 g, 81.3 mmol) and the solution was stirred until homogeneous. To this solution was added di-tert-butyl dicarbonate (18.22 g, 83.5 mmol)
20 in 1,4-dioxane (77 mL) dropwise, and the resulting solution was stirred for 72 hours at ambient temperature. The solution was concentrated in vacuo and the resulting aqueous solution was washed with ethyl ether. The aqueous solution was acidified to
25 pH=2 with concentrated HCl. The solution was extracted with ethyl ether and concentrated in vacuo provided a white solid. Recrystallization (ethyl

-640-

acetate) provided N-Boc-isonipecotic acid as a white solid (10 g, 54 %).

Part B: To a solution of the N-Boc-isonipecotic acid of part A (2.14 g, 9.33 mmol) in
5 dichloromethane (19 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.82 g, 9.49 mmol), N-hydroxybenzotriazole (1.32 g, 9.77 mmol) and 1-(2,3-xylyl)piperazine monohydrochloride (2.47 g, 10.89
10 mmol). After 30 minutes diisopropylethylamine (0.74 mL, 20.7 mmol) was added, and the solution was stirred for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with 1M HCl, saturated NaHCO₃ and
15 saturated NaCl. The solution was dried over MgSO₄. Recrystallization (ethyl acetate/hexane) provided the amide as an off-white solid (2.65 g, 71 %).

Part C: To a solution of the amide of part B (1.0 g, 3.75 mmol) in dichloromethane (5 mL) was
20 added trifluoroacetic acid (5 mL) and the solution was stirred for 15 minutes. The solution was concentrated in vacuo and the resulting oil was dissolved into N,N-dimethylacetamide (10 mL). To this solution was added the product of Example 398,
25 Part A (979 mg, 2.50 mmol) and cesium carbonate (3.67 g, 11.25 mmol) and the solution was heated at one hundred and ten degrees Celsius for 17 hours. The solution was partitioned between ethyl acetate and H₂O. The organic layer was washed with H₂O and
30 saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the piperidine compound as a white solid (1.89 g, quantitative yield). MS(CI) MH⁺ calculated for C₃₅H₄₈N₄O₅S: 637, found 637.

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Part D: To a solution of the piperidine compound of part C (1.89 g) in ethanol (8 mL) and tetrahydrofuran (8 mL) was added sodium hydroxide (1.0 g, 25 mmol) in H₂O (5 mL). The solution was
5 heated to fifty degrees Celsius for 8 hours and at sixty-two degrees Celsius for 8 hours. The solution was concentrated in vacuo and the residue was diluted with H₂O and acidified to pH = 3 with 3M HCl. The resulting precipitate was collected by vacuum
10 filtration to provide the acid as a white solid (1.16 g, 65 %). MS(CI) MH⁺ calculated for C₃₃H₄₄N₄O₅S: 609, found 609.

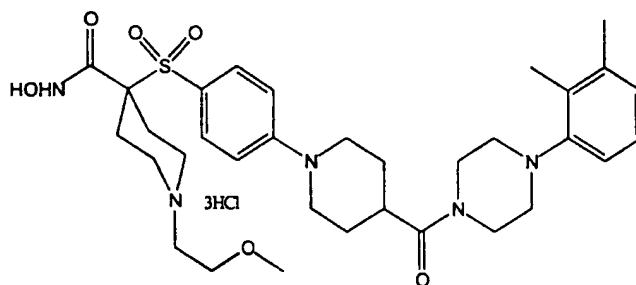
Part E: To a solution of the acid of part D (1.16 g, 1.62 mmol) in N,N-dimethylformamide (10
15 mL) were added N-hydroxybenzotriazole (262 mg, 1.94 mmol), 4-methylmorpholine (0.90 mL, 8.2 mmol) and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (284 mg, 2.4 mmol). After stirring for 45 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
20 hydrochloride (334 mg, 2.2 mmol) was added and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H₂O and the organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄.
25 Trituration (dichloromethane) provided the protected hydroxamate as a white solid (850 mg, 75 %). MS(CI) MH⁺ calculated for C₃₈H₅₃N₅O₆S: 708, found 708.
Analytical calculation for C₃₈H₅₃N₅O₆S•0.5H₂O: C, 63.66; H, 7.59; N, 9.77; S, 4.47. Found: C, 63.68; H, 7.54;
30 N, 9.66; S, 4.67.

Part F: To a solution of the protected hydroxamate of part E (746 mg, 1.07 mmol) in methanol (10 mL) was added 4M HCl in 1,4-dioxane (10 mL) and

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the solution was stirred for one hour. The resulting solid was collected by vacuum filtration and washed with ethyl ether to provide the title compound as a white solid (650 mg, 83 %). MS(CI) MH^+ calculated for $C_{33}H_{45}N_5O_5S$: 624, found 624. HRMS calculated for $C_{33}H_{45}N_5O_5S$: 624.3220, found 624.3253. Analytical calculation for $C_{33}H_{45}N_5O_5S \cdot 3.5HCl \cdot H_2O$: C, 51.82; H, 6.59; N, 9.16. Found: C, 52.04; H, 6.30; N, 8.96.

10 Example 413: Preparation of 4-[[4-[4-[[4-(2,3-dimethylphenyl)-1-piperazinyl]carbonyl]-1-piperidinyl]phenyl]sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidine-carboxamide,
15 trihydrochloride



Part A: To a solution of the isonipecotic
20 acid (10.5 g, 81.3 mmol) in H_2O (325 mL) was added sodium carbonate (8.37 g, 81.3 mmol) and the solution was stirred until homogeneous. To this solution was added di-tert-butyl dicarbonate (18.22 g, 83.5 mmol) in 1,4-dioxane (77 mL) dropwise and the resulting
25 solution was stirred for 72 hours at ambient temperature. The solution was concentrated in vacuo and the resulting aqueous solution was washed with

-643-

ethyl ether. The aqueous solution was acidified to pH=2 with concentrated HCl. The solution was extracted with ethyl ether and concentration in vacuo provided a white solid. Recrystallization (ethyl acetate) provided N-Boc-isonipecotinic acid as a white solid (10 g, 54 %).

Part B: To a solution of the N-Boc-isonipecotinic acid of part A (2.14 g, 9.33 mmol) in dichloromethane (19 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.82 g, 9.49 mmol), N-hydroxybenzotriazole (1.32 g, 9.77 mmol) and 1-(2,3-xylyl)piperazine monohydrochloride (2.47 g, 10.89 mmol). After 30 minutes, diisopropylethylamine (0.74 mL, 20.7 mmol) was added and the solution was stirred for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with 1M HCl, saturated NaHCO₃ and saturated NaCl. The solution was dried over MgSO₄. Recrystallization (ethyl acetate/hexane) provided the amide as an off-white solid (2.65 g, 71 %).

Part C: To a solution of the amide of part B (965 mg, 2.41 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL) and the solution was stirred for 15 minutes. The solution was concentrated in vacuo and the resulting oil was dissolved into N,N-dimethylacetamide (10 mL). To this solution were added ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (600 mg, 1.61 mmol) and cesium carbonate (2.75 g, 8.43 mmol), and the solution was heated at one hundred and ten degrees Celsius for 20 hours. The solution was partitioned between ethyl

-644-

acetate and H₂O. The organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the piperidine compound as a white solid (1.26 g, quantitative yield). MS(CI) MH⁺ calculated for C₃₅H₅₀N₄O₆S: 655, found 655.

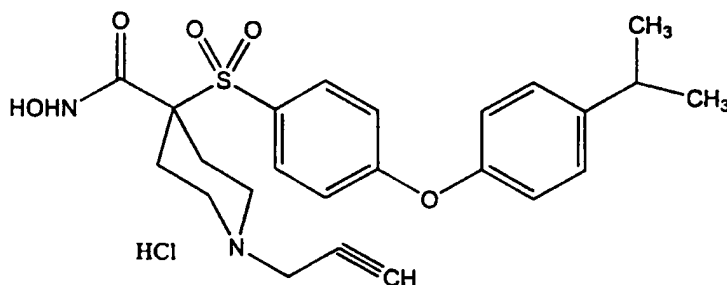
Part D: To a solution of the piperidine compound of part C (1.26 g) in ethanol (5 mL) and tetrahydrofuran (5 mL) was added sodium hydroxide (644 mg, 16 mmol) in H₂O (5 mL). The solution was heated to sixty degrees Celsius for 8 hours and at sixty-two degrees Celsius for 8 hours. The solution was concentrated in vacuo and the residue was diluted with H₂O and acidified to pH = 3 with 3M HCl. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (650 mg, 65 %). MS(CI) MH⁺ calculated for C₃₃H₄₆N₄O₆S: 627, found 627.

Part E: To a solution of the acid of part D (620 g, 0.94 mmol) in N,N-dimethylformamide (10 mL) were added N-hydroxybenzotriazole (152 mg, 1.13 mmol), 4-methylmorpholine (0.52 mL, 4.7 mmol) and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (165 mg, 1.4 mmol). After stirring for 45 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (252 mg, 1.32 mmol) was added and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H₂O, and the organic layer was washed with H₂O and saturated NaCl, and dried over Na₂SO₄. Concentration in vacuo provided the protected hydroxamate as a white solid (641 mg, 94 %). MS(CI) MH⁺ calculated for C₃₈H₅₅N₅O₇S: 726, found 726.

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Part F: To a solution of the protected hydroxamate of part E (630 mg, 0.87 mmol) in methanol (8 mL) was added 4M HCl in 1,4-dioxane (10 mL) and the solution was stirred for one hour. The resulting solid was collected by vacuum filtration and washed with ethyl ether to provide the title compound as a white solid (624 mg, 83 %). MS(CI) MH^+ calculated for $C_{33}H_{47}N_5O_6S$: 642, found 642.

10 Example 414: Preparation of N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part E (6.0 g, 15.4 mmol) and powdered K_2CO_3 (8.0 g, 38.5 mmol) in N,N-dimethylformamide (70 mL) was added 4-isopropyl phenol (5.24 g, 38.5 mmol) at ambient temperature, and the solution was heated to ninety degrees Celsius for 32 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the diaryl ether as light yellow gel (6.89 g, 87%).

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Part B: To a solution of diaryl ether of part A (6.89 g, 14.7 mmol) in ethanol (14 mL) and tetrahydrofuran (14 mL) was added NaOH (5.88 g, 147 mmol) in H₂O (28 mL) from an addition funnel at
5 ambient temperature. The solution was then heated to sixty degrees Celsius for 17 hours and ambient temperature for 24 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether and acidified
10 to pH = 2. Vacuum filtration of white precipitation provided the acid as a white solid (6.56 g, quantitative yield).

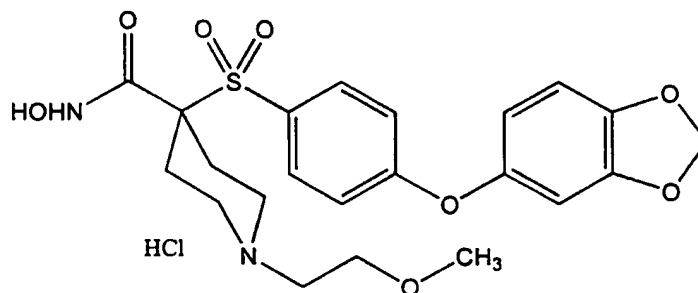
Part C: To the solution of acid of part B (6.56 g, 14.86 mmol), N-methyl morpholine (6.5 mL, 59.4 mmol), 1-hydroxybenzotriazole (6.0 g, 44.6 mmol) and O-tetrahydropyranyl hydroxyl amine (3.5 g, 29.7 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.5 g, 44.6 mmol), and the solution
20 was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃, H₂O and dried over MgSO₄. Concentration in vacuo and
25 chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (8.03 g, quantitative yield).

Part D: To a solution of 4N HCl in dioxane (37
30 mL, 149 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (8.03 g, 14.9 mmol) in methanol (5 mL) and dioxane (15 mL) and the solution was stirred at ambient

-647-

temperature for 3 hours. Concentration in vacuo and trituration with diethyl ether provided the title compound as a white solid (5.0 g, 71.1%). Analytical calculation for $C_{24}H_{28}N_2O_5S \cdot HCl \cdot 0.9H_2O$: C, 56.61; H, 6.10; N, 5.50; S, 6.30. Found: C, 56.97; H, 6.05; N, 5.41; S, 5.98. HRMS MH^+ calculated for $C_{24}H_{28}N_2O_5S$: 457.1797, found 457.1816.

Example 415: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl)sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, monohydrochloride



15

Part A: To a solution of the product of Example 9, Part D (25 g, 67.3 mmol) and powdered K_2CO_3 (23.3 g, 169 mmol) in N,N-dimethylformamide (150 mL) was added sesamol (23.2 g, 168 mmol) at ambient temperature and solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the

-648-

desired diaryl ether as light yellow gel (33.6 g, 93.6%).

Part B: To a solution of diaryl ether of part A (4.0 g, 7.4 mmol) in dichloromethane (7 mL) cooled to
5 zero degrees Celsius was added trifluoroacetic acid (7 mL) and the solution was stirred at ambient temperature for 2 hours. Concentration *in vacuo* provided the amine trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate
10 salt and K_2CO_3 (3.6 g, 26 mmol) in N,N-dimethylformamide (50 mL) was added 2-bromoethyl methyl ether (1.8 mL, 18.7 mmol) and the solution was stirred at ambient temperature for 36 hours. The N,N-dimethylformamide was evaporated under high
15 vacuum and residue was diluted with ethyl acetate. The organic layer was washed with water and dried over Mg_2SO_4 . Concentration *in vacuo* provided the methoxyethyl amine as a light yellow gel (3.7 g, quantitative yield).

20 Part C: To a solution of methoxyethyl amine of part B (3.7 g, 7.5 mmol) in ethanol (7 mL) and tetrahydrofuran (7 mL) was added NaOH (3.0 g, 75 mmol) in H_2O (15 mL) from an addition funnel at ambient temperature. The solution was then heated to
25 sixty degrees Celsius for 19 hours and ambient temperature for 12 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of the white precipitate
30 provided the acid as a white solid (4.0 g, quantitative yield).

Part D: To a solution of the acid of part C (4.0 g, 7.5 mmol), N-methyl morpholine (3.3 mL, 30

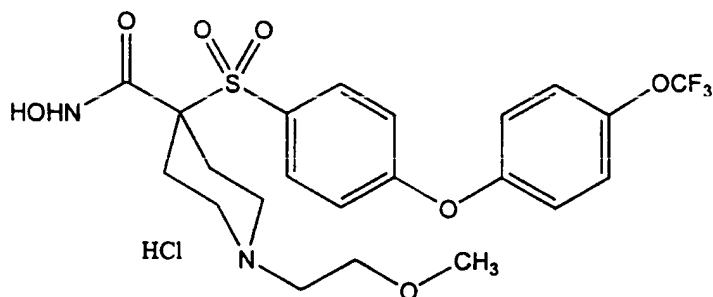
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mmol), 1-hydroxybenzotriazole (3.0 g, 22.5 mmol) and
O-tetrahydropyranyl hydroxyl amine (1.8 g, 15 mmol)
in N,N-dimethylformamide (100 mL) was added 1-[3-
(dimethylamino)propyl]-3-ethylcarbodiimide
5 hydrochloride (4.3 g, 22.5 mmol), and the solution
was stirred at ambient temperature for 4 days. The
solution was concentrated under high vacuum and the
residue was dissolved in ethyl acetate. The organic
layer was washed with saturated aqueous NaHCO₃, H₂O
10 and dried over Mg₂SO₄. Concentration in vacuo and
chromatography on silica eluting with ethyl
acetate/hexane provided the tetrahydropyranyl-
protected hydroxamate as a white foam (2.40 g,
57.1%).

15 Part E: To a solution of 4N HCl in dioxane (11
mL, 43 mmol) was added a solution of the
tetrahydropyranyl-protected hydroxamate of part D
(2.4 g, 4.3 mmol) in methanol (2 mL) and dioxane (6
mL) and the solution was stirred at ambient
20 temperature for 3 hours. Concentration in vacuo and
trituration with ether provided hydroxamate
hydrochloride salt as a white solid (1.88 g, 85.8%).
Analytical calculation for C₂₂H₂₆N₂O₈S.HCl.H₂O: C,
49.58; H, 5.48; N, 5.26; S, 6.02. Found: C, 49.59;
25 H, 5.53; N, 5.06; S, 5.71. HRMS MH⁺ calculated for
C₂₂H₂₆N₂O₈S: 479.1488, found 479.1497.

Example 416: Preparation of N-hydroxy-1-(2-
methoxyethyl)-4-[[4-[4-(trifluoro-
30 methoxy)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,
monohydrochloride

-650-



Part A: To a solution of the product of Example 9, Part D (30 g, 161 mmol) in dichloromethane (50 mL) cooled to zero degrees Celsius was added
5 trifluoroacetic acid (25 mL) and the solution was stirred at ambient temperature for 1 hour. Concentration in vacuo provided the amine trifluoroacetate salt as a light yellow gel. To the
10 solution of the trifluoroacetate salt and K₂CO₃ (3.6 g, 26 mmol) in N,N-dimethylformamide (50 mL) cooled to zero degrees Celsius was added 2-bromoethyl methyl ether (19 mL, 201 mmol), and solution was stirred at ambient temperature for 36 hours. Then, N,N-
15 dimethylformamide was evaporated under high vacuum and the residue was diluted with ethyl acetate. The organic layer was washed with water and dried over MgSO₄. Concentration in vacuo provided the methoxyethyl amine as a light yellow gel (26.03 g,
20 86.8%).

Part B: To a solution of methoxyethyl amine (6.0 g, 16.0 mmol) of part A and powdered K₂CO₃ (4.44 g, 32 mmol) in N,N-dimethylformamide (30 mL) was added 4-(trifluoromethoxy)phenol (5.72 g, 32 mmol) at ambient
25 temperature and the solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was

-651-

dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H₂O and dried over MgSO₄.

Chromatography on silica eluting with ethyl acetate/hexane provided trifluoromethoxy

5 phenoxyphenyl sulfone as a light yellow gel (7.81 g, 91.5%).

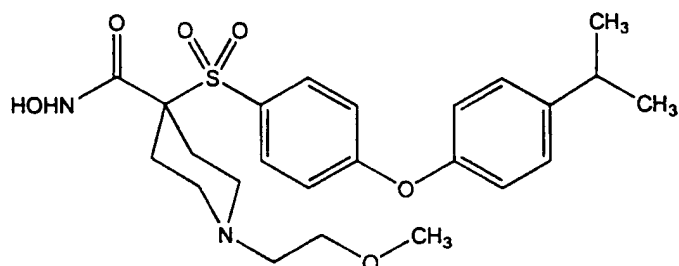
Part C: To a solution of trifluoromethoxy phenoxyphenyl sulfone of part B (7.81 g, 14.7 mmol) in ethanol (14 mL) and tetrahydrofuran (14 mL) was
10 added NaOH (5.88 g, 147 mmol) in H₂O (28 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted
15 with ether and acidified to pH=2. Vacuum filtration of white precipitation provided the acid as a white solid (5.64 g, 73.3%).

Part D: To a solution of the acid of part C (5.64 g, 10.8 mmol), N-methyl morpholine (4.8 mL,
20 43.1 mmol), 1-hydroxybenzotriazole (4.38 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.5 g, 21.6 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.2 g, 32.4 mmol), and the solution
25 was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃, H₂O and dried over MgSO₄. Concentration in vacuo and
30 chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (6.65 g, quantitative yield).

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Part E: To a solution of 4N HCl in dioxane (28 mL, 110 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part D (6.65 g, 11.03 mmol) in methanol (3 mL) and dioxane
5 (9 mL) and was stirred at ambient temperature for 3 hours. Concentration in vacuo and trituration with diethyl ether provided the title compound as a white solid (4.79 g, 78.2%). Analytical calculation for $C_{22}H_{25}N_2O_7SF_3 \cdot HCl \cdot 0.5H_2O$: C, 46.85; H, 4.83; N, 4.97; S,
10 5.69. Found: C, 46.73; H, 4.57; N, 4.82; S, 5.77.

Example 417: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(1-methylethyl)-phenoxy]phenyl]sulfonyl]-4-
15 piperidinecarboxamide, monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-
20 piperidinecarboxylate (1.47 g, 3.9 mmol) and powdered K_2CO_3 (1.6 g, 11.7 mmol) in N,N-dimethylformamide (15 mL) was added 4-isopropylphenol (1.07 g, 7.8 mmol) at ambient temperature and the solution was heated to
25 ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$.

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Chromatography on silica eluting with ethyl acetate/hexane provided the diaryl ether as a light yellow gel (1.77 g, 92.2%).

Part B: To a solution of diaryl ether of part A
5 (1.77 g, 3.6 mmol) in ethanol (3.5 mL) and tetrahydrofuran (3.5 mL) was added NaOH (1.46 g, 36 mmol) in H₂O (7 mL) at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and
10 diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (1.39 g, 83.7%).

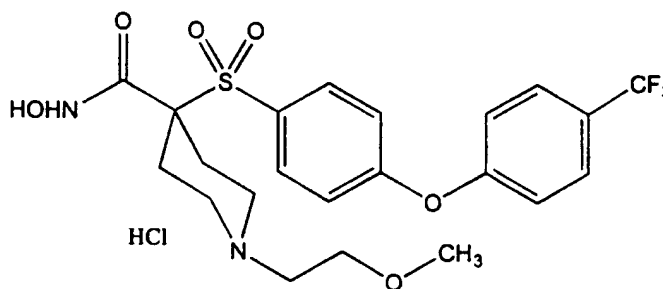
Part C: To the solution of the acid of part B
15 (1.39 g, 3.0 mmol), N-methyl morpholine (1 mL, 9 mmol), 1-hydroxybenzotriazole (1.22 g, 9 mmol) and O-tetrahydropyranyl hydroxyl amine (0.72 g, 6.0 mmol) in N,N-dimethylformamide (90 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
20 hydrochloride (1.72 g, 9.0 mmol), and solution was stirred at ambient temperature for 48 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃, H₂O
25 and dried over MgSO₄. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (1.65 g, 98.2%).

30 Part D: To a solution of 4N HCl in dioxane (7.35 mL, 29.4 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (1.65 g, 2.94 mmol) in methanol (1 mL) and dioxane (3

-654-

mL), and the solution was stirred at ambient temperature for 3 hours. Concentration in vacuo and trituration with diethyl ether provided the title compound as a white solid (1.2 g, 79.5%). Analytical calculation for $C_{24}H_{32}N_2O_6S \cdot HCl \cdot 0.5H_2O$: C, 55.22; H, 6.56; N, 5.37; S, 6.14. Found: C, 55.21; H, 6.41; N, 5.32; S, 6.18.

Example 418: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]phenyl]sulfonyl}-4-piperidinecarboxamide, monohydrochloride



15

Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (6 g, 16.0 mmol) and powdered K_2CO_3 (4.44 g, 32 mmol) in N,N-dimethylformamide (50 mL) was added 4-trifluoromethylphenol (5.72 g, 32 mmol) at ambient temperature, and the solution was heated to ninety degrees Celsius for 48 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (2.66 g, 32.1%).

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Part B: To a solution of the diaryl ether of part A (1.5 g, 2.9 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was added NaOH (1.22 g, 29 mmol) in H₂O (6 mL) at ambient temperature. The solution was then heated to sixty degrees Celsius for 18 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the desired acid as a white solid (1.0 g, 70.9%).

Part C: To the solution of the acid of part B (1.0 g, 2.05 mmol), N-methyl morpholine (0.68 mL, 6.1 mmol), 1-hydroxybenzotriazole (0.84 g, 6.15 mmol) and O-tetrahydropyranyl hydroxyl amine (0.5 g, 4.1 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.18 g, 6 mmol), and solution was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated NaHCO₃, H₂O and dried over MgSO₄. Concentration *in vacuo* and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (1.16 g, 96.7%).

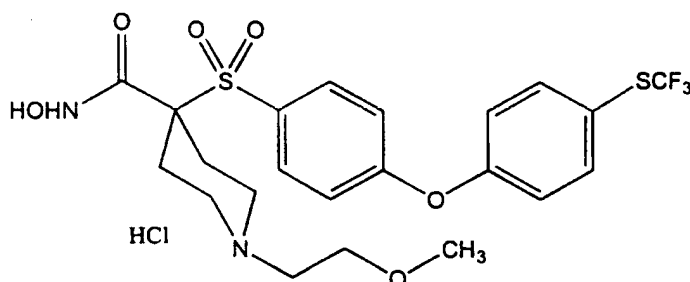
Part D: To a solution of 4N HCl in dioxane (5 mL, 20 mmol)) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (1.16 g, 2 mmol) in methanol (1 mL) and dioxane (3 mL) and was stirred at ambient temperature for 3 hours. Concentration *in vacuo* and trituration with diethyl ether provided the title compound as a white solid (0.79 g, 74.5%). Analytical calculation for

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$C_{22}H_{25}N_2O_6SF_3 \cdot HCl$: C, 49.03; H, 4.86; N, 5.20; S, 5.95.

Found: C, 48.85; H, 4.60; N, 5.22; S, 6.13.

Example 419: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-[(trifluoromethyl)thio]phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



10

Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (5 g, 13.4 mmol) and powdered K₂CO₃ (3.7 g, 27 mmol) in N,N-dimethylformamide (20 mL) was added 4-(trifluoromethylthio)phenol (3.9 g, 20 mmol) at ambient temperature, and solution was heated to ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum, and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H₂O and dried over MgSO₄. Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (5.94 g, 81.04%).

Part B: To a solution of the diaryl ether of part A (5.94 g, 210 mmol) in ethanol (10 mL) and tetrahydrofuran (10 mL) was added NaOH (4.34 g, 108 mmol) in H₂O (20 mL) dropwise at ambient temperature.

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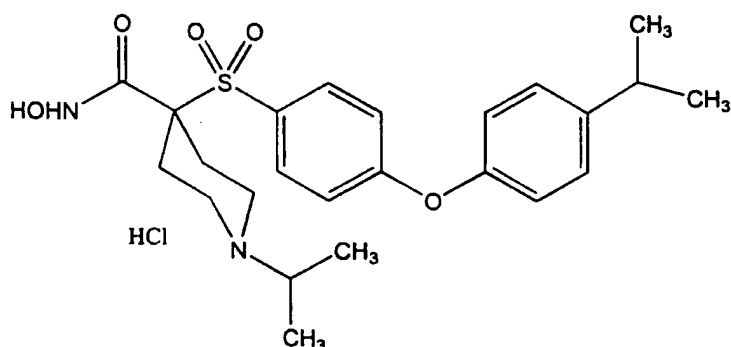
The solution was then heated to sixty degrees Celsius for 24 hours and ambient temperature for another 24 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (5.5 g, quantitative yield).

Part C: To the solution of the acid of part B (5.5 g, 10.8 mmol), N-methyl morpholine (3.6 mL, 32.4 mmol), 1-hydroxybenzotriazole (4.4 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.6 g, 21.8 mmol) in N,N-dimethylformamide (200 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.2 g, 32.4 mmol), and the solution was stirred at ambient temperature for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated aqueous NaHCO₃, H₂O and dried over MgSO₄. Concentration in vacuo and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (4.66 g, 69.8%).

Part D: To a solution of 4N HCl in dioxane (20 mL, 79 mmol)) was added a solution of the tetrahydropyranyl-protected hydroxamate of part C (4.65 g, 7.9 mmol) in methanol (2.5 mL) and dioxane (8 mL) and was stirred at ambient temperature for 3 hours. Concentration in vacuo and trituration with diethyl ether provided the title compound as a white solid (3.95 g, 92.1%). Analytical calculation for C₂₂H₂₅N₂O₆S₂F₃.HCl: C, 46.27; H, 4.59; N, 4.91; S, 11.23. Found: C, 46.02; H, 4.68; N, 4.57; S, 11.11.

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Example 420: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-[4-(1-methylethyl)-phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide,
5 monohydrochloride



- 10 Part A: To a solution of the product of Example 9, Part D (30 g, 161 mmol) in dichloromethane (40 mL) cooled to zero degrees Celsius was added trifluoroacetic acid (30 mL), and the solution was stirred at ambient temperature for 1 hour.
- 15 Concentration *in vacuo* provided the trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate salt and triethylamine (28 mL, 201 mmol) in dichloromethane (250 mL) cooled to zero degrees Celsius, were added acetone (24 mL, 320 mmol)
- 20 and sodium triacetoxyborohydride (68 g, 201 mmol) in small portions followed by addition of acetic acid (18.5 mL, 320 mmol), and solution was stirred at ambient temperature for 48 hours. Then, the dichloromethane was evaporated under high vacuum and
- 25 the residue was diluted with diethyl ether. The organic layer was washed with 1N NaOH, water and

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dried over MgSO_4 . Concentration *in vacuo* provided the isopropyl amine as a light yellow gel (21.03 g, 72.8%).

Part B: To a solution of isopropyl amine (4 g, 11.2 mmol) of part A and powdered K_2CO_3 (3.09 g, 22.4 mmol) in N,N-dimethylformamide (30 mL) was added 4-isopropylphenol (3.05 g, 22 mmol) at ambient temperature and the solution was heated to ninety degrees Celsius for 25 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over MgSO_4 . Chromatography on silica eluting with ethyl acetate/hexane provided the desired diaryl ether as a light yellow gel (5.10 g, 96.2%).

Part C: To a solution of the diaryl ether of part B (5.10 g, 10.77 mmol) in ethanol (10 mL) and tetrahydrofuran (10 mL) was added NaOH (4.3 g, 108 mmol) in H_2O (20 mL) from an addition funnel at ambient temperature. The solution was then heated to sixty degrees Celsius for 24 hours and at ambient temperature for another 24 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with diethyl ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the desired acid as a white solid (4.80 g, quantitative yield).

Part D: To the solution of the acid of part C (4.80 g, 10.8 mmol), N-methyl morpholine (3.6 mL, 32.4 mmol), 1-hydroxybenzotriazole (4.4 g, 32.4 mmol) and O-tetrahydropyranyl hydroxyl amine (2.6 g, 21.6 mmol) in N,N-dimethylformamide (100 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

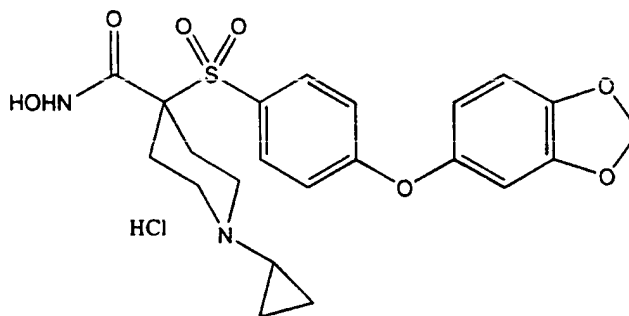
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hydrochloride (6.17 g, 32.4 mmol), and the solution was stirred at ambient temperature for 7 days. The solution was filtered to eliminate the unreacted starting material and the filtrate was concentrated under high vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous NaHCO_3 , H_2O and dried over MgSO_4 . Concentration in vacuo and chromatography on silica eluting with ethyl acetate/hexane provided the tetrahydropyranyl-protected hydroxamate as a white foam (2.45 g, 41.7%).

Part E: To a solution of 4N HCl in dioxane (11.2 mL, 45 mmol) was added a solution of the tetrahydropyranyl-protected hydroxamate of part D (2.45 g, 11.03 mmol) in methanol (4 mL) and dioxane (8 mL) and was stirred at ambient temperature for 3 hours. Concentration in vacuo and tituration with diethyl ether provided the title compound as a white solid (2.01 g, 89.7%). Analytical calculation for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5\text{S} \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 56.96; H, 6.77; N, 5.54; S, 6.34. Found: C, 56.58; H, 6.71; N, 5.44; S, 6.25.

Example 421: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-1-cyclopropyl-N-hydroxy-4-piperidinecarboxamide, monohydrochloride

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Part A : To a solution of the product of Example 9, Part D (9.0 g, 22.0 mmol) in DMF (30 mL) was added K₂CO₃ (4.55 g, 33 mmol), and sesamol (4.55 g, 33 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with 10% ethyl acetate/hexane provided the desired ester as an oil (9.3 g, 79%). HRMS MH⁺ calculated for C₂₆H₃₁NSO₉: 534.1798, found 534.1796..

Part B: To a solution of the ester of part A (9.3 g, 17 mmol) in ethyl acetate (100 mL) cooled to zero degrees C was bubbled gaseous HCl for 10 minutes. The reaction was stirred at this temperature for 0.5 hours. The solution was concentrated in vacuo to give the hydrochloride salt (7.34 g, 92%). MS MH⁺ calculated for C₂₁H₂₃NSO₇: 434.1273, found 434.1285..

Part C: To a solution of the hydrochloride salt of part B (7.34 g, 15.6 mmol) in methanol (60 mL) was added acetic acid (8.94 mL, 156 mmol), a portion (about 2 g) of 4-Å molecular sieves, (1-ethoxycyclopropyl)-oxytrimethyl silane (18.82 mL, 93.6 mmol) and sodium cyanoborohydride (4.41 g, 70.2

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mmol). The solution was refluxed for 8 hours. The precipitate was removed by filtration and the filtrate concentrated in vacuo. The residue was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with 100% ethyl acetate) provided the desired cyclopropyl amine as a solid (7.9 gm, 100%). MS MH⁺ calculated for C₂₄H₂₇NSO₇: 474.1586, found 474.1599.

Part D: To a solution of cyclopropyl amine from part C (7.9 g, 16.7 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.68 g, 166.8mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=3. The resulting precipitate was filtered to give desired carboxylic acid (6.14 g, 76%). MS MH⁺ calculated for C₂₂H₂₅NSO₇: 446.1273. Found 446.1331.

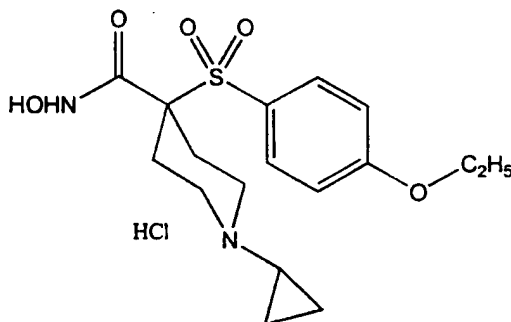
Part E: To a solution of the carboxylic acid of part D (6.14 g, 12.7mmol) in DMF (60 mL) was added 1-hydroxybenzotriazole (2.06 g, 15.2 mmol), N-methyl morpholine (4.2 mL, 38.0 mmol) and O-tetrahydropyranyl hydroxyl amine (2.23 g, 19.0 mmol) followed by 1,3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.41 g, 17.8 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with 40% ethyl acetate/hexane

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provided the desired tetrahydropyranyl-protected hydroxamate as a solid (6.67 g, 96%).

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (6.67 g, 12.0 mmol)
5 in dioxane (70 mL) was added 4 N HCl/dioxane (6.6 mL). After stirring at ambient temperature for 3 hours, the solution was concentrated in vacuo. Chromatography on a C18 reverse phase column, eluting with acetonitrile/(HCl)water, provided a white solid
10 (4.21 gm, 69%). MS MH^+ calculated for $C_{22}H_{24}N_2SO_7$: 461.1382. Found 461.1386.

Example 422: Preparation of 1-cyclopropyl-4-[[4-(4-ethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,
15 monohydrochloride



20 Part A: To a solution of the product of Example 9, Part D (8.0 g, 19.2 mmol) in DMF (30 mL) was added K_2CO_3 (4.00 g, 28.8 mmol) and 4-ethoxyphenol (3.99 g, 28.8 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was
25 diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$, filtered and concentrated

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in vacuo. Chromatography on silica gel eluting with 10% ethyl acetate/hexane provided the desired ester as an oil (9.62 g, 94 %). MS MH^+ calculated for $C_{27}H_{35}NSO_8$: 534.2162. Found 534.2175.

5 Part B: To a solution of ester of part A (9.62 g, 18 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 5 minutes. The reaction was stirred at this temperature for 0.5 hours. The solution was then
10 concentrated in vacuo to give the hydrochloride salt (8.1 g, 96%). MS MH^+ calculated for $C_{22}H_{27}NSO_6$: 434.1637. Found 434.1637.

Part C: To a solution of the hydrochloride salt of part B (8.1 g, 17.2 mmol) in methanol (70 mL) was
15 added acetic acid (9.86 mL, 172 mmol), a portion of 4-Å molecular sieves (ca. 2 g), (1-ethoxycyclopropyl)-oxytrimethyl silane (20.7 mL, 103 mmol) and sodium cyanoborohydride (4.86 g, 77.4 mmol). The solution was refluxed for 8 hours. The
20 precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with 1 N NaOH, saturated NaCl and dried over $MgSO_4$, filtered and
25 concentrated in vacuo. Trituration with diethyl ether provided the desired cyclopropyl amine as a white solid (6.84 g, 84%).

Part D: To a solution of cyclopropyl amine from part C (6.84g, 14.0 mmol) in ethanol (50 mL) and
30 tetrahydrofuran (50 mL) was added a solution of NaOH (5.60 g, 140 mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the

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aqueous residue was acidified to pH=3. Filtration gave the desired acid (6.07 g, 88%). MS MH⁺ calculated for C₂₂H₂₇NSO₆: 446. Found 446.

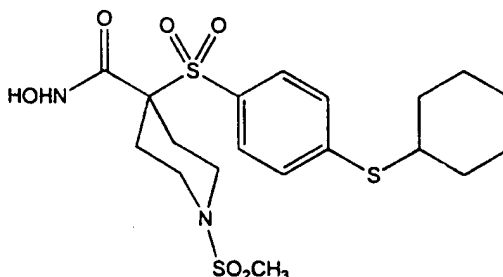
Part E: To a solution of the acid of part D
5 (6.07g, 12.6 mmol) in DMF (60 mL) was added 1-hydroxybenzotriazole (2.04 g, 15.1 mmol), N-methylmorpholine (4.15 mL, 37.8 mmol) and O-tetrahydropyranyl hydroxyl amine (2.21 g, 18.9 mmol) followed by 1,3-(dimethylamino)propyl-3-
10 ethylcarbodiimide hydrochloride (3.38 g, 17.6 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄,
15 filtered and concentrated in vacuo. Chromatography on silica gel eluting with 60% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white foam (6.29 g, 92%). MS MH⁺ calculated for C₂₈H₃₆N₂SO₇: 545.2321. Found 545.2316.

20 Part F: To a solution of the tetrahydropyranyl-protected hydroxamate of part E (2.84 g, 5.0 mmol) in dioxane (40 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated in vacuo. Trituration
25 of the resulting solid with diethyl ether and filtration gave the desired hydroxamate as a white solid (2.33 g, 90%). MS M⁺ calculated for C₂₃H₂₈N₂SO₆: 460.1677. Found 460.1678.

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Example 423: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-1-(methylsulfonyl)-4-piperidinecarboxamide

5



Part A: To a solution of the product of Example 9, Part D (10.0 g, 24.0 mmol) in DMF (20 mL) was added K₂CO₃ (4.99 g, 36.0 mmol), cyclohexyl mercaptan (4.40 g, 36.0 mmol). The solution was stirred at ninety degrees Celsius for 48 hrs. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Trituration with ethanol provided the desired sulfide as a white solid (7.16 g, 58%).

Part B: To a solution of sulfide from part B (9.46 g, 18.5 mmol) in ethanol (30 mL) and tetrahydrofuran (30 mL) was added a solution of NaOH (7.39 g, 185 mmol) in water (15 mL) and the solution was heated at sixty-five degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH = 3.5. The resulting white solid was collected by filtration washed with H₂O and ethyl ether to give desired carboxylic acid (8.57 g, 95%).

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Part C: To a solution of carboxylic acid of part B (8.3 g, 17.0 mmol) in ethyl acetate (200 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 15 min. The reaction was then stirred at this
5 temperature for 0.5 hour. The solution was concentrated in vacuo to afford a residue which was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (7.03 g, 98%). MS MH⁺ calculated for C₁₈H₂₅NS₂O₄: 384.1303. Found
10 384.1318.

Part D: To a solution of the hydrochloride salt of part C (1.0 g, 2.4 mmol) was added N-methyl morpholine (654 mL, 5.9 mmol) followed by mesyl chloride (280 mL, 3.6 mmol) in methylene chloride (20
15 mL). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (400 mL) and extracted with methylene chloride. The organic layer was washed with water, saturated NaCl and dried over MgSO₄, filtered and concentrated in
20 vacuo to yield the desired methanesulfonamide as a foam (1.0 g, quantitative yield)

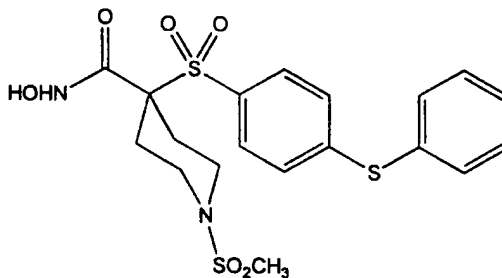
Part E: To a solution of the methanesulfonamide of part D (1.3 g, 2.9 mmol) in DMF (30 mL) was added 1-hydroxybenzotriazole (474 mg, 3.5 mmol), N-methyl
25 morpholine (956 mL, 8.7 mmol), tetrahydropyranyl hydroxyl amine (509 mg, 4.3 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (778 mg, 4.06 mmol). The solution was stirred at ambient temperature for 18 hours. The
30 solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica

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gel eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white foam (1.05 g, 82%).

Part F: To a solution of the tetrahydropyranyl-protected hydroxamate of part E (1.05 g, 1.97 mmol) in dioxane (30 mL) was added 4 N HCl/dioxane (10 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated in vacuo. Chromatography on C18 reverse phase column eluting with acetonitrile/(HCl) water provided a white solid (602 mg, 64%). MS M^+ for $C_{19}H_{28}N_2S_3O_6$: 477, found 477.

Example 424: Preparation of N-hydroxy-1-(methylsulfonyl)-4-[[4-(phenylthio)-phenyl]sulfonyl]-4-piperidinecarboxamide



Part A: To a solution of the product of Example 9, Part D (40.0 g, 96.0 mmol) in DMF (200 mL) was added K_2CO_3 (20 g, 144 mmol) and thiophenol (22.2 g, 144 mmol). The solution was stirred at ambient temperature for 24 hrs. The solution was then diluted with H_2O (1 L) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatography (on silica,

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elueting with 15% ethyl acetate/hexane) provided the desired sulfide as a white solid (44.4 g, 91%).

Part B: To a solution of sulfide of part A (31.2 g, 6.6 mmol) in ethyl acetate (500 mL) cooled
5 to zero degrees Celsius was bubbled gaseous HCl for 30 minutes. The reaction was stirred at this temperature for 1.5 hours. The solution was concentrated in vacuo and resulting solid was triturated with diethyl ether to provide the
10 hydrochloride salt as a white solid (26.95 g, 96%).

Part C: To a solution of the hydrochloride salt of part B (2.0 g, 4.7 mmol), were added N-methyl morpholine (1.29 mL, 11.7 mmol), followed by mesyl chloride (550 mL, 7.05 mmol) in methylene chloride
15 (35 mL). The solution was stirred at ambient temperature for 48 hours. The solution was diluted with H₂O (400 mL) and extracted with methylene chloride. The organic layer was washed with water, saturated NaCl and dried over MgSO₄, filtered and
20 concentrated in vacuo to yield the desired methanesulfonamide as a white solid (2.17 gm, 96%).

Part D: To a solution of the methane sulfonamide from part C (2.1 g, 4.3 mmol) in ethanol (25 mL) and tetrahydrofuran (25 mL) was added a
25 solution of NaOH (1.72 g, 43 mmol) in water (10 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=3.5. The resulting precipitate was filtered to give the
30 desired carboxylic acid as a white solid (2.1 g, quantitative yield).

Part E: To a solution of the carboxylic acid of part D (1.98 g, 4.3 mmol) in DMF (30 mL) were added

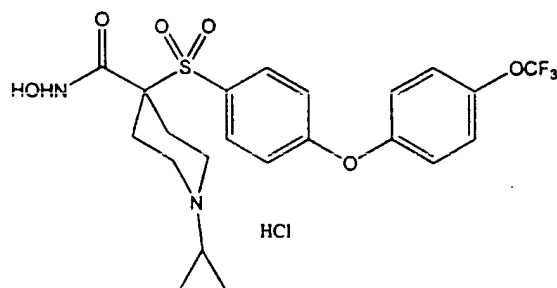
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1-hydroxybenzotriazole (705 mg, 5.2 mmol), N-methyl morpholine (1.54 mL, 12.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (755 mg, 6.5 mmol) followed by 1-3-(dimethylamino) propyl]-3-ethyl carbodiimide hydrochloride (1.17 g, 6.1 mmol). The solution was stirred at ambient temperature for 5 days. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on C18 reverse phase column, eluting with acetonitrile/(HCl) water provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (1.86 g, 80%). HRMS MH⁺ calculated for C₂₄H₃₀N₂S₃O₇: 555.1293, found 555.1276.

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (1.86 g, 3.5 mmol) in dioxane (30 mL) and methanol (10 mL) was added 4 N HCl/dioxane (20 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated in vacuo. Chromatography on a C18 reverse phase column eluting with acetonitrile/(HCl) water provided the title compound as a white solid (1.48 gm, 91%). HRMS MH⁺ calculated for C₁₉H₂₂N₂S₃O₆: 471.0718 Found 471.0728.

Example 425: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-phenyl]sulfonyl]-4-piperidine-carboxamide, monohydrochloride

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Part A: To a solution of the product of Example 398, Part A (6.97 g, 19.6 mmol) in DMF (500 mL) was added K_2CO_3 (3.42 g, 18.0 mmol) and 4-(trifluoromethoxy)-phenol (3.7 g, 24.8 mmol). The solution was stirred at ninety degrees Celsius for 40 hours. The solution was diluted with H_2O (600 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated in vacuo to afford the desired diaryl ether as an oil (8.5 g, quantitative). HRMS MH^+ calculated for $C_{24}H_{26}NSO_6F_3$: 514.1511. Found 514.1524.

Part B: To a solution of diaryl ether from part A (8.4 g, 16.4 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.54 g, 164 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo to remove most of organic solvents and the aqueous residue was acidified to pH=4.0. The resulting precipitate was filtered to give the desired filtered to give the hydrochloride salt as a white solid (5.01 g, 63%). HRMS MH^+ calculated for $C_{22}H_{22}NSO_6F_3$: 486.1198, found 486.1200.

Part C: To a solution of the hydrochloride salt of part B (5.0 g, 10.3 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.65 g, 12.3 mmol), N-

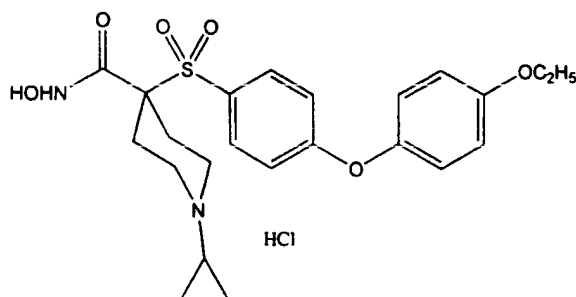
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methyle morpholine (3.4 mL, 30.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.8 g, 15.4 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.60 g, 12.3 mmol). The solution was stirred at ambient temperature for 42 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel, eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (5.41 g, 89%).

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (5.4 g, 9.2 mmol) in dioxane (80 mL) and methanol (20 mL) was added 4 N HCl/dioxane (50 mL). The reaction was stirred at ambient temperature for 2.5 hours, the solution was concentrated in vacuo. Trituration with diethyl ether afforded the title compound as a white solid (4.02 g, 81%). HRMS MH⁺ calculated for C₂₂H₂₃N₂SO₆F₃: 501.1307, found 501.1324.

Example 426: Preparation of 1-cyclopropyl-4-[(4-ethoxyphenyl) sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the product of Example 398, Part A (5.87 g, 16.5 mmol) in DMF (50 mL) was added K_2CO_3 (3.42 g, 24.7 mmol) and α,α,α -(trifluoromethyl)-p-cresol (4.01g, 24.7 mmol). The solution was stirred at ninety degrees Celsius for 48 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product, containing a large percentage of starting material (8.39 g). To this material (8.39 g) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (6.75 g, 169 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=3.5. The resulting precipitate was filtered to give the desired hydrochloride salt as a waxy solid (5.04 g, 64%).

Part B: To a solution of the hydrochloride salt of part A (5.0 g, 10.3 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.73 g, 12.8 mmol), N-methyl morpholine (3.5 mL, 31.8 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.86 g, 15.9 mmol) followed by 1-3-(dimethylamino)propyl]-

- 674 -

3-ethylcarbodiimide hydrochloride (2.84 g, 14.8 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate.

5 The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated *in vacuo*. Chromatography on silica gel eluting with 30% ethyl acetate/hexane provided the desired

10 tetrahydropyranyl-protected hydroxamate as a white solid (1.5 g, 32%).

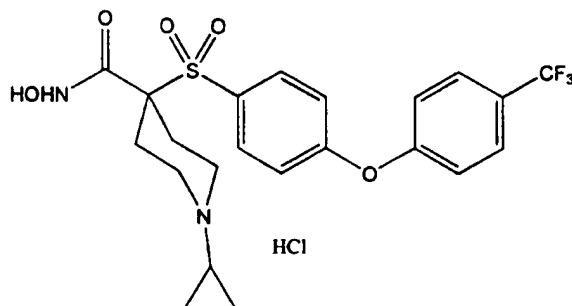
Part C: To a solution of tetrahydropyranyl-protected hydroxamate of part D (1.5 g, 3.3mmol) in dioxane (30 mL) and methanol (15 mL) was added 4 N HCl/dioxane (50 mL). The reaction was stirred at

15 ambient temperature for 2 hours, then the solution was concentrated *in vacuo*. Trituration of the residue with diethyl ether afforded the title compound as a white solid (1.09g, 81%). MS MH⁺ for C₁₇H₂₄N₂SO₅: 369 found 369.

20

Example 427: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide,

25 monohydrochloride



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Part A: To a solution of the product of Example 398, Part A (5.96 g, 15.0 mmol) in DMF (100 mL) was added K_2CO_3 (12.34 g, 38.0 mmol) and α,α,α -

5 trifluoromethyl phenol (3.65 g, 22.5 mmol). The solution was stirred ninety degrees Celsius for 28 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over $MgSO_4$

10 , filtered and concentrated in vacuo to afford desired aryl ether as an oil (7.54 g, quantitative)

Part B: To a solution of aryl ether from part A (7.54 g, 15.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH

15 (6.06 g, 151.0 mmol) in water (20 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=2.0. The resulting precipitate was filtered to give the

20 desired hydrochloride salt as a white solid (7.98 g, quantitative). MS MH^+ calculated for $C_{22}H_{22}NSO_5F_3$: 470, found 470.

Part C: To a solution of the hydrochloride salt of part B (7.60 g, 15.0 mmol) in DMF (100 mL) were

25 added 1-hydroxybenzotriazole (2.44 g, 18.0 mmol), N-methyl morpholine (3.4 mL, 30.9 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.63 g, 22.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.02 g, 21.0

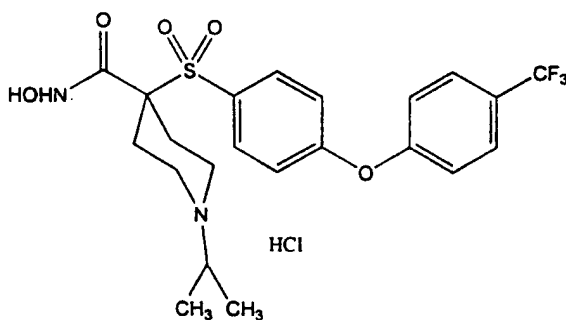
30 mmol). The solution was stirred at ambient temperature for 96 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and

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dried over MgSO_4 , filtered and concentrated in vacuo. Chromatography on silica eluting with 30% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (5.93g, 69%).

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (3.8 g, 6.7 mmol) in dioxane (100 mL) was added 4 N HCl/dioxane (30 mL). The reaction was stirred at ambient temperature for 2 hours, then the solution was concentrated in vacuo. Trituration with diethyl ether afforded the title compound as a white solid (3.33 g, 96%). MS MH^+ calculated for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{SO}_5\text{F}_3$: 485, found 485.

Example 428: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-(trifluoromethyl)-phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (30.0 g, 80.8 mmol) in methylene chloride (100 mL) was added trifluoroacetic acid (30 mL) in methylene chloride (40 mL). The solution was stirred at ambient temperature for two hours. The solution

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was concentrated in vacuo. To the residue dissolved in methylene chloride (150 mL) at zero degrees Celsius were added triethylamine (28.0 mL, 277 mmol), acetone (24.0 mL, 413 mmol), sodium cyanoborohydride
5 (68 g, 323.1 mmol) and acetic acid (18.5 mL, 308 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The solution was diluted with 1N NaOH and extracted with ethyl ether. The organic layer was washed with 1N NaOH, water,
10 saturated NaCl and dried over MgSO_4 , filtered and concentrated in vacuo to provided the desired isopropylamine (21.03 g, 72%).

Part B: To a solution of the isopropylamine of part A (4.04 g, 11.0 mmol) in DMF (50 mL) was added
15 CsCO_3 (10.75g, 33.3 mmol) and α,α,α -trifluoro-p-cresol (2.67g, 16.5 mmol). The solution was stirred at ninety degrees Celsius for 40 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water,
20 saturated NaCl and dried over MgSO_4 , filtered and concentrated in vacuo. Chromatography on silica gel, eluting with 30% ethyl acetate/hexane, provided the desired diaryl ether as an oil (5.35 g, 97%).
HRMS MH^+ calculated for $\text{C}_{24}\text{H}_{28}\text{NSO}_5\text{F}_3$: 500.1640, found:
25 500.1678.

Part C: To a solution of the diaryl ether from part B (5.3 g, 10.6 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (4.2 g, 106.0 mmol) in water (25 mL) and the solution
30 was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=3.0. The resulting precipitate was filtered to give the

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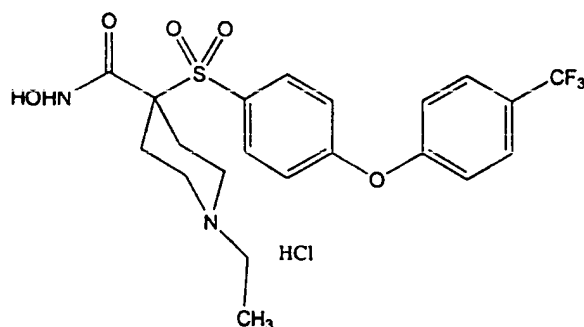
desired hydrochloride salt as a white solid (5.38 g, quantitative). MS MH^+ calculated for $C_{22}H_{24}NSO_5F_3$: 472.1406, found 471.472.1407.

Part D: To a solution of the hydrochloride salt
5 of part C (5.4 g, 10.6 mmol) in DMF (90 mL) were added 1-hydroxybenzotriazole (1.72 g, 12.3 mmol), N-methyl morpholine (3.5 mL, 32.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (1.87 g, 15.9 mmol) followed by 1-3-(dimethylamino)propyl]-
10 3-ethylcarbodiimide hydrochloride (2.8 g, 15.0 mmol). The solution was stirred at ambient temperature for 144 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and
15 dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatography on silica gel, eluting with 2% methanol/ethyl acetate, provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (2.74 g, 45%). HRMS MH^+ calculated for
20 $C_{27}H_{33}N_2SO_5F_3$: 571.2090, found 571.2103

Part E: To a solution of tetrahydropyranyl-protected hydroxamate of part D (2.7 g, 4.7 mmol) in dioxane (50 mL) was added 4 N HCl/dioxane (20 mL). The reaction was stirred at ambient temperature for 2
25 hours. Filtration afforded the title compound as a white solid (2.08 g, 84%). MS MH^+ calculated for $C_{22}H_{25}N_2SO_5F_3$: 487, found 487.

Example 429: Preparation of 1-ethyl-N-hydroxy-4-[[4-
30 [4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide,
monohydrochloride

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Part A: To a solution of the product of Example 9, Part D (48 g, 115.0 mmol) in ethyl acetate (750 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 45 minutes, and stirred at that temperature for 7 hours. The solution was concentrated *in vacuo* to afford a residue that was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (32.76 g, 81%).

Part B: To a solution of hydrochloride salt of part A (15.8 g, 45.0 mmol) in DMF (75 mL) was added K₂CO₃ (12.4 g, 90.0 mmol) and bromoethane (3.4 mL, 45.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (200 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over MgSO₄, filtered and concentrated *in vacuo* to provide the desired ethyl amine as an oil (15.4 g, quantitative).

Part C: To a solution of ethyl amine of part B (5.2 g, 15.0 mmol) in DMF (50 mL) was added CsCO₃ (12.21 g, 37.5 mmol) and α,α,α -trifluoro-*p*-cresol (3.65 g, 23.0 mmol). The solution was stirred ninety degrees Celsius for 25 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water,

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saturated NaCl and dried over MgSO_4 , filtered and concentrated in vacuo. Chromatography on silica gel, eluting with 20% ethyl acetate/hexane, provided the desired diaryl ether as an oil (7.3 g, quantitative yield).

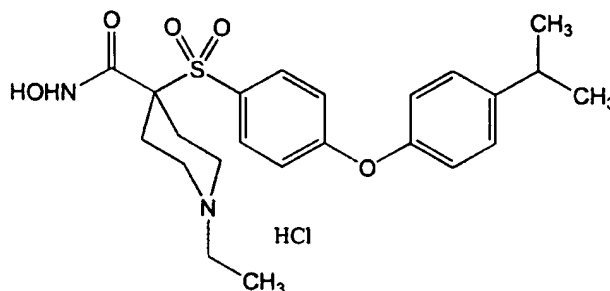
Part D: To a solution of diaryl ether from part C (7.3 g, 15.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (6.0 g, 150 mmol) in water (30 mL), and the solution was heated at sixty degrees Celsius for 16 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=4.0. The resulting precipitate was filtered to give the desired hydrochloride salt as a white solid (5.96 g, 80%). HRMS MH^+ calculated for $\text{C}_{21}\text{H}_{22}\text{NSO}_5\text{F}_3$: 458.1249, found 458.1260

Part E: To a solution of the hydrochloride salt of part D (5.96 g, 12.0 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (1.96 g, 14.0 mmol), N-methyl morpholine (3.9 mL, 36.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.11 g, 18.0 mmol) followed by 1-3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (3.24 g, 17.0 mmol). The solution was stirred at ambient temperature for 168 hours. The insoluble material was removed by filtration and the filtrate was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO_4 , filtered and concentrated in vacuo. Chromatography on silica gel eluting with 70% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (2.80 g, 41%).

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Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (2.8 g, 5.0 mmol) in dioxane (80 mL) was added 4 N HCl/dioxane (20 mL). The reaction was stirred at ambient temperature for 5 hours, and the solution was concentrated in vacuo. Trituration with diethyl ether afforded the title compound as a white solid (2.08 g, 84%). MS MH⁺ calculated for C₂₁H₂₃N₂SO₅F₃: 473, found 473.

- 10 Example 430: Preparation of 1-ethyl-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part D (48 g, 115.0 mmol) in ethyl acetate (750 mL) cooled to zero degrees Celsius was bubbled gaseous HCl for 45 minutes. The reaction was stirred at this temperature for 7 hours. The solution was concentrated in vacuo to afford a residue which was triturated with diethyl ether to afford the desired hydrochloride salt as a white solid (32.8 g, 81%).

25 Part B: To a solution of the hydrochloride salt of part A (15.8 g, 45.0 mmol) in DMF (75 mL) was added K₂CO₃ (12.4 g, 90.0 mmol) and bromoethane (3.4

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mL, 45.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (200 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated
5 NaCl and dried over MgSO₄, filtered and concentrated in vacuo to afford the desired ethyl amine as an oil (15.4 g, quantitative).

Part C: To a solution of ethyl amine of part B (5.2 g, 15.0 mmol) in DMF (50 mL) was added CsCO₃
10 (12.2 g, 37.5 mmol) and 4-isopropylphenol (3.15 g, 23.0 mmol). The solution was stirred at ninety degrees Celsius for 5 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water,
15 saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with 20% ethyl acetate/hexane provided the desired diaryl ether as an oil (6.2 g, 95%). HRMS MH⁺ calculated for C₂₅H₃₃N₃SO₅: 460.2158, found: 460.2160.

20 Part D: To a solution of diaryl ether from part C (6.2 g, 13.0 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (5.2 g, 130 mmol) in water (30 mL) and the solution was heated at sixty degrees Celsius for 16 hours.
25 The solution was concentrated in vacuo and the aqueous residue was acidified to pH = 4.0. The resulting precipitate was filtered and washed with H₂O and diethyl ether to give desired hydrochloride salt (6.0 g, quantitative). HRMS MH⁺ calculated for
30 C₂₃H₂₉NSO₅: 432.1845, found 432.1859.

Part E: To a solution of the hydrochloride salt of part D (6.08 g, 13.0 mmol) in DMF (80 mL) were added 1-hydroxybenzotriazole (2.11 g, 15.6 mmol), N-

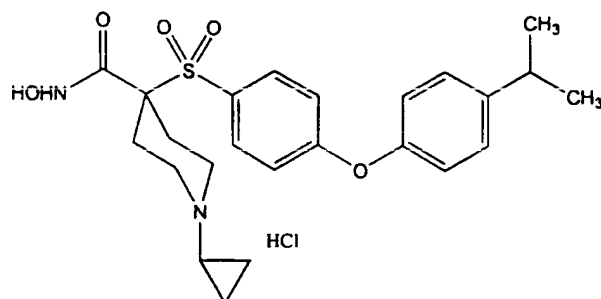
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methyl morpholine (4.3 mL, 39.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (2.28 g, 19.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.49 g, 18.2 mmol). The solution was stirred at ambient temperature for 168 hours. Insoluble material was removed by filtration and the filtrate was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with 50% ethyl acetate/hexane provided the desired tetrahydropyranyl-protected hydroxamate as a white solid (1.7 g, 25%). HRMS MH⁺ calculated for C₂₈H₃₈N₂SO₆: 531.2529, found 531.2537.

Part F: To a solution of tetrahydropyranyl-protected hydroxamate of part E (1.7 g, 3.0 mmol) in dioxane (60 mL) was added 4 N HCl/dioxane (10 mL). The reaction was stirred at ambient temperature for 4 hours, and the solution was concentrated in vacuo. Chromatography on C18 reverse phase column eluting with acetonitrile/(HCl)water provided the title compound as a white solid (860 mg, 59%). HRMS MH⁺ calculated for C₂₃H₃₀N₂SO₅: 447.1954, found 447.1972

Example 431: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(1-methylethyl)phenoxy]phenyl]-sulfonyl]-4-piperidine-carboxamide, monohydrochloride

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Part A: To a solution of the product of Example 398, Part A (4.0 g, 10.2 mmol) in DMF (40 mL) was added K₂CO₃ (12.46 g, 38.0 mmol) and 4-isopropylphenol (4.99 g, 15.3 mmol). The solution was stirred at ninety degrees Celsius for 24 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica eluting with 30% ethyl acetate/hexane provided the desired diaryl ether as a white solid (3.89g, 76%). HRMS MH⁺ calculated for C₂₆H₃₃NSO₅: 472.2158, found: 472.2171.

Part B: To a solution of diaryl ether from part A (3.89 g, 8.20 mmol) in ethanol (40 mL) and tetrahydrofuran (40 mL) was added a solution of NaOH (3.30 g, 82.5 mmol) in water (25 mL) and the solution was heated at sixty degrees Celsius for 18 hours. The solution was concentrated in vacuo to remove most of the organic solvents and the aqueous residue was acidified to pH=3.0. The resulting precipitate was filtered and washed with H₂O and ethyl ether to give desired hydrochloride salt (7.98 g, quantitative) as a white solid. MS MH⁺ calculated for C₂₄H₂₉NSO₅: 444, found: 444.

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Part C: To a solution of the hydrochloride salt of part B (3.6 g, 7.0 mmol) in DMF (70 mL) were added 1-hydroxybenzotriazole (1.22 g, 9.0 mmol), N-methyl morpholine (2.3 mL, 21.0 mmol) and O-

5 tetrahydropyranyl hydroxyl amine hydrochloride (1.23 g, 10.5 mmol) followed by 1-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.01 g, 10.4 mmol). The solution was stirred at ambient temperature for 15 days. The solution was diluted

10 with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel, eluting with 15% ethyl acetate/hexane, provided the desired

15 tetrahydropyranyl-protected hydroxamate as a white solid (3.51 g, 92%). HRMS MH⁺ calculated for C₂₉H₃₈N₂SO₆: 543.2529, found 543.2539.

Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C

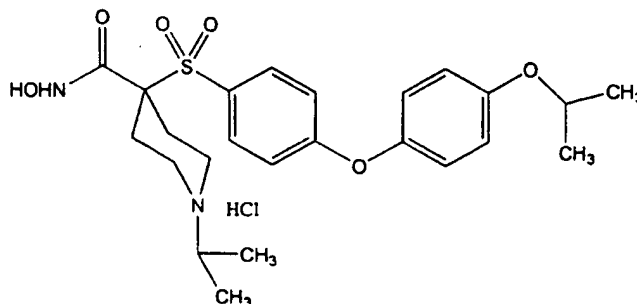
20 (3.51 g, 6.0 mmol) in methanol (10 mL) and dioxane (200 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 2.5 hours, the solution was concentrated in vacuo. Trituration with diethyl ether afforded the title compound as a white

25 solid (2.56 g, 86%). MS MH⁺ calculated for C₂₄H₃₀N₂SO₅: 459.1875, found 459.1978.

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Example 432: Preparation of N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]phenyl]sulfonyl]-1-(1-methylethyl)-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(1-methylethyl)-4-piperidinecarboxylate (2.0 g, 5.4 mmol) in N,N-dimethylformamide (10 mL) was added 4-isopropoxyphenol, which may be prepared according to the procedure of *J. Indian Chem. Soc.*, **73**, 1996, 507-511, (1.63 g, 10.7 mmol) and cesium carbonate (7 g, 21.5 mmol) and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane to afford the desired aryl ether (1.06 g, 39%).

Part B: To a solution of the aryl ether (1.06 g, 2.1 mmol) in ethanol (20 mL) and water (20 mL) was added sodium hydroxide (0.84 g, 21 mmol) and the mixture was heated to 65 degrees Celsius for 16

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hours. The solvents were then removed in vacuo. Water (50 mL) was added and the mixture was again concentrated in vacuo and the resulting mixture was acidified with 2 N HCl to pH=4-5. The solid
5 precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (3.13 g, 100%).

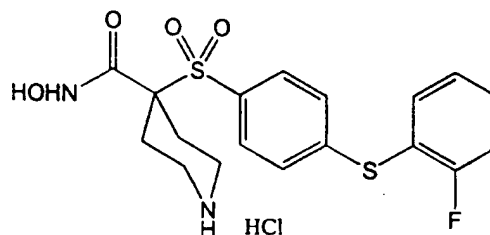
Part C: A solution of the carboxylic acid of part B (1.0 g, 2.0 mmol) in thionyl chloride (5 mL)
10 was refluxed for 2 hours. The solvent was removed in vacuo. To the resulting residue in DMF (10 mL) was added N-methyl morpholine (0.66 mL, 6.0 mmol) and O-tetrahydropyranyl hydroxyl amine hydrochloride (351 mg, 3.0 mmol). The solution was stirred at
15 ambient temperature for 18 hours. The suspension was filtered and the filtrate was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over MgSO₄, filtered and concentrated in vacuo.
20 Chromatography on silica gel eluting with 90% ethyl acetate/hexane provided the desired tetrahydropyran-protected hydroxamate as a white solid (280 mg, 23%). HRMS MH⁺ calculated for C₂₉H₄₀N₂SO₇: 561.2634, found 561.2653.

25 Part D: To a solution of tetrahydropyranyl-protected hydroxamate of part C (275 mg, 0.48 mmol) in dioxane (15 mL) was added 4 N HCl/dioxane (5 mL). After stirring at ambient temperature for 2 hours, the solution was concentrated in vacuo. Trituration
30 with diethyl ether and filtration of the resulting solid gave the title compound as a white solid (193 mg, 76%). MS MH⁺ calculated for C₂₄H₃₂N₂SO₆: 477, found 477.

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Example 433: Preparation of 4-[[4-[(2-fluorophenyl)-thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the product of Example 9, Part D (6.0 g, 14.4 mmol) in N,N-
10 dimethylformamide (30 mL) were added 2-fluorothiophenol (2.22 g, 17.3 mmol) and potassium carbonate (2.40 g, 17.3 mmol), and the resulting suspension was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with
15 ethyl acetate (200 mL) and washed with 1 N sodium hydroxide (200 mL) and brine (3X). Concentration of the organic phase afforded a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:4), to afford the
20 desired aryl sulfide (8.0 grams, 100%) as a white solid.

Part B: To a solution of the ethyl ester of part A (8.0 g, 15 mmol) in ethanol (90 mL) and water (20 mL) was added sodium hydroxide (6.1 g, 152
25 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Volatile organics were removed in vacuo and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with

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ethyl acetate. The combined organic extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (4.92 g, 68%).

5 Part C: To a solution of the carboxylic acid of part B (4.92 g, 9.93 mmol) in N,N-dimethylformamide (100 mL) were added 4-methylmorpholine (1.52 g, 15.0 mmol), N-hydroxybenzotriazole (1.62 g, 12.0 mmol) and 1-[3-
10 (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.70 g, 14.1 mmol), followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (2.24 g, 15.0 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to
15 a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel afforded the protected hydroxamate derivative (4.9 mg, 83%).

20 Part D: Hydrogen chloride gas was bubbled for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C (4.9 g, 8.24 mmol) in ethyl acetate (30 mL). The mixture was then allowed to stand at ambient temperature for 2 hours,
25 after which time the solvent was removed *in vacuo*. Fresh ethyl acetate (30 mL) was added and then removed *in vacuo*, and this procedure was repeated. Ethyl acetate (50 mL) was then added and the solid was collected by filtration to afford a solid that
30 was purified by reverse-phase chromatography,, eluting with acetonitrile/water (gradient of 20/80 up to 100% acetonitrile), to afford the title compound (1.9 g, 43%). Analytical calculation for

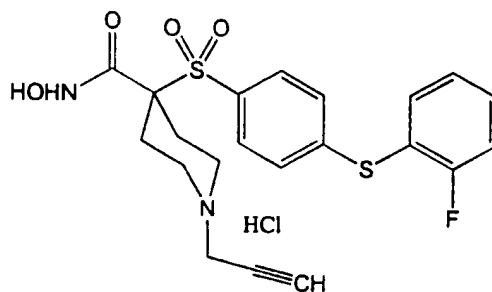
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$C_{18}H_{19}FN_2O_4S_2 \cdot HCl$: C, 48.37; H, 4.51; N, 6.27; Cl, 7.93. Found: C, 48.14; H, 4.33; N, 6.21; Cl, 8.64. HRMS (ESI) MH^+ calculated for $C_{18}H_{19}FN_2O_4S_2$: 411.0849, found 411.0844.

5

Example 434: Preparation of 4-[[4-[(2-fluorophenyl)-thio]phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the product of Example 9, Part F (4.46 g, 12.6 mmol) in N,N-dimethylformamide (30 mL) were added 2-fluorothiophenol (1.94 g, 15.1 mmol) and potassium carbonate (2.09 g, 15.1 mmol), and the resulting suspension was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with ethyl acetate (200 mL) and washed with 1 N sodium hydroxide (200 mL) and brine (3X). Concentration of the organic phase afforded the desired aryl sulfide (5.2 grams, 90%).

Part B: To a solution of the ethyl ester of part A (5.1 g, 11.4 mmol) in ethanol (90 mL) and water (30 mL) was added sodium hydroxide (5.0 g, 125 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Organics were removed *in vacuo*

-691-

and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (4.5 g, 94%).

Part C: To a solution of the carboxylic acid of part B (4.5 g, 11.0 mmol) in N,N-dimethylformamide (50 mL) were added 4-methylmorpholine (1.62 g, 16.0 mmol), N-hydroxybenzotriazole (1.73 g, 12.8 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.87 g, 14.9 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (2.39 g, 16.0 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel afforded the protected hydroxamate derivative that was used directly in the next step.

Part D: Hydrogen chloride gas was bubbled for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C in ethyl acetate (30 mL). The mixture was then allowed to stand at ambient temperature for 2 hours after which time the solvent was removed in vacuo. Fresh ethyl acetate (30 mL) was added and then removed in vacuo, and this procedure was repeated. Ethyl acetate (50 mL) was then added and the solid was collected by filtration to afford a solid which was purified by reverse-phase chromatography eluting with acetonitrile/water

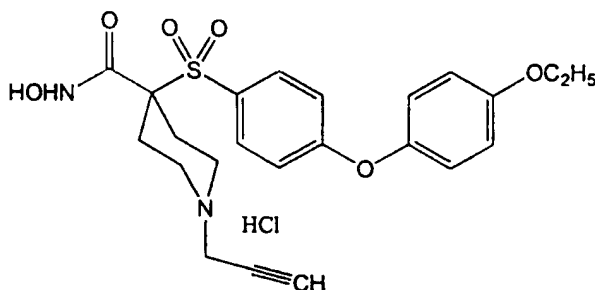
-692-

(gradient of 20/80 up to 100% acetonitrile) to afford the title compound (1.85 g, 35% for parts C and D). HRMS (ESI) MH^+ calculated for $C_{21}H_{21}FN_2O_4S_2$: 449.1005, found 449.1023.

5

Example 435: Preparation of 4-[[4-(4-ethoxyphenoxy)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

10



Part A: To a solution of the product of Example 9, Part F (8.00 g, 22.6 mmol) in N,N-dimethylformamide (50 mL) were added 4-ethoxyphenol (9.38 g, 70 mmol) and cesium carbonate (22.8 g, 70 mmol), and the resulting suspension was heated at 75 degrees Celsius for 20 hours. The reaction mixture was then diluted with ethyl acetate (1000 mL) and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:2), to afford the desired diaryl ether (10.5 grams, 99%).

Part B: To a solution of the ethyl ester of part A (10.5 g, 22.3 mmol) in ethanol (70 mL) and water (60 mL) was added sodium hydroxide (8.9 g, 222 mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. Volatile organics were removed

-693-

in vacuo and the resulting aqueous mixture was acidified with 2 N HCl to pH=3-4. Solid sodium chloride was added and the mixture was extracted with ethyl acetate. The combined organic extracts were
5 washed with brine and dried with magnesium sulfate. Removal of the solvent afforded the desired carboxylic acid (10 g, 100%).

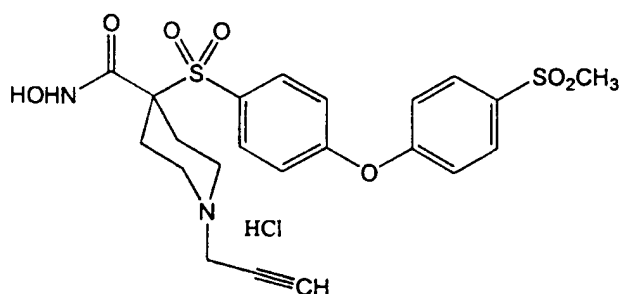
Part C: To a solution of the carboxylic acid of part B (10 g, 22.5 mmol) in N,N-
10 dimethylformamide (50 mL) were added 4-methylmorpholine (3.42 g, 33.8 mmol), N-hydroxybenzotriazole (3.66 g, 27.1 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.05 g, 31.6 mmol) followed by O-
15 (tetrahydro-2H-pyran-2-yl)hydroxylamine (5.05 g, 33.8 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration
20 and purification by chromatography on silica gel, eluting with ethyl acetate/hexane (1:1), afforded the protected hydroxamate derivative (6.5 g, 53%) which was used directly in the next step.

Part D: To a solution of the protected
25 hydroxamate of part C in methanol/1,4-dioxane (1:3, 70 mL) was added 4 N HCl/1,4-dioxane (30 mL) and the solution was stirred at ambient temperature for 4 hours. The solvent was then removed in vacuo. Methanol (40 mL) was added and then removed in vacuo.
30 Diethyl ether (100 mL) was added and the resulting solid was collected by filtration to afford the title compound (4.3 g, 72%). Analytical calculation for $C_{23}H_{26}N_2O_6S \cdot HCl \cdot H_2O$: C, 53.85; H, 5.70; N, 5.46; Cl,

-694-

6.91; S, 6.25. Found: C, 53.65; H, 5.62; N, 5.41; Cl, 6.86; S, 6.48. MS (ESI) MH^+ calculated for $C_{23}H_{26}N_2O_6S$: 459, found 459.

- 5 Example 436: Preparation of N-hydroxy-4-[[4-[4-(methylsulfonyl)phenoxy]phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 9, Part F (2.5 g, 6.4 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylsulphonylphenol (3.5 g, 20.3 mmol) and cesium carbonate (8.7 g, 27 mmol), and the resulting suspension was heated at 90 degrees Celsius for 16 hours. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ethyl acetate (500 mL) and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to afford the desired aryl ether (2.5 grams, 77%).

25 Part B: To a solution of the ethyl ester of part A (2.5 g, 4.9 mmol) in ethanol (50 mL) and water (30 mL) was added sodium hydroxide (2.0 g, 49 mmol) and the mixture was heated to 65 degrees

-695-

Celsius for 8 hours. The solvents were removed in vacuo. Water (50 mL) was added, the mixture was again concentrated in vacuo and the resulting mixture was acidified with 2 N HCl to pH=4-5. The solid
5 precipitate was collected by filtration to afford the desired carboxylic acid (1.57 g, 67%).

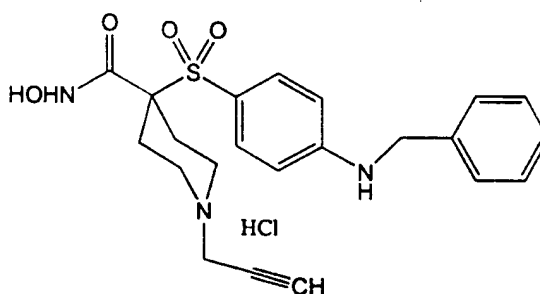
Part C: To a solution of the carboxylic acid of part B (1.57 g, 3.3 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.5 g, 4.9 mmol), N-hydroxybenzotriazole (0.53 g, 3.9 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.88 g, 4.6 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.74, 4.9
15 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel,
20 eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (1.5 g, 79%), which was used directly in the next step.

Part D: To a solution of the protected hydroxamate of part C (1.5 g, 2.60 mmol) in
25 methanol/1,4-dioxane (1:3, 40 mL) was added 4 N HCl/1,4-dioxane (10 mL), and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed in vacuo. Methanol (30 mL) was added and then removed in vacuo. Diethyl ether (100 mL)
30 was added and the resulting solid was collected by filtration to afford the title compound (1.35 g, 98%). Analytical calculated for $C_{22}H_{24}N_2O_7S_2 \cdot HCl$: C, 49.95; H, 4.76; N, 5.30; Cl, 6.70; S, 12.12. Found:

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C, 49.78; H, 4.56; N, 5.25; Cl, 6.98; S, 11.98. HRMS (ESI) MH⁺ calculated for C₂₂H₂₄N₂O₇S₂: 493.1103, found 493.1116.

- 5 Example 437: Preparation of N-hydroxy-4-[[4-
[(phenylmethyl)amino]phenyl]sulfonyl]-
1-(2-propynyl-4-piperidinecarboxamide,
monohydrochloride



Part A: To a solution of the product of Example 9, Part F (2.5 g, 6.4 mmol) in N,N-dimethylformamide (30 mL) were added benzylamine (3.44 g, 32.1 mmol) and cesium carbonate (10.5 g, 32.3 mmol) and the resulting suspension was heated at 100 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500 mL) and washed with water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane (1:1), to afford the desired benzyl aniline derivative (2.5 grams, 88%).

25 Part B: To a solution of the ethyl ester of part A (2.5 g, 5.67 mmol) in ethanol (50 mL) and water (30 mL) was added sodium hydroxide (2.27 g, 56.7 mmol), and the mixture was heated to 65 degrees

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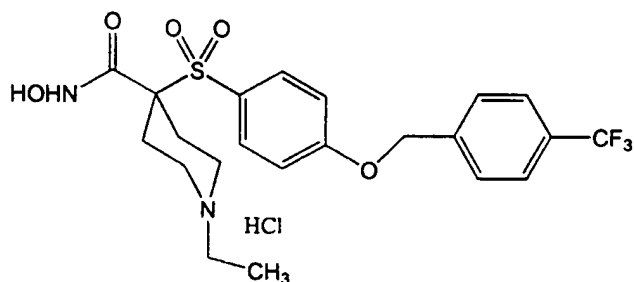
Celsius for 8 hours. The solvents were removed in vacuo. Water (50 mL) was added and the mixture was again concentrated in vacuo and the resulting mixture was acidified with 2 N HCl to pH = 4-5. The solid
5 precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (2.3 g, 98%).

Part C: To a solution of the carboxylic acid of part B (2.3 g, 5.57 mmol) in N,N-
10 dimethylformamide (15 mL) were added 4-methylmorpholine (0.85 g, 8.36 mmol), N-hydroxybenzotriazole (0.9 g, 6.69 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 g, 7.8 mmol) followed by O-
15 (tetrahydro-2H-pyran-2-yl)hydroxylamine (1.25, 8.36 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue which was dissolved in ethyl acetate and washed with water and brine. Concentration and
20 purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the next step.

Part D: Hydrogen chloride gas was bubbled
25 for 10 minutes through an ice bath-cooled solution of the protected hydroxamate of part C in ethyl acetate (50 mL). The solvent was then removed in vacuo. Ethyl acetate (100 mL) was added and then removed in vacuo. Ethyl acetate (100 mL) was then added and the
30 resulting solid was collected by filtration to afford the title compound (1.6 g, 62% for steps C and D). HRMS (ESI) MH^+ calculated for $C_{22}H_{25}N_3O_4S$: 428.1644, found 428.1652.

-698-

Example 438: Preparation of 1-ethyl-N-hydroxy-4-[[4-
[[4-[trifluoromethyl]phenyl]methoxy]-
phenyl]sulfonyl]-4-piperidine-
5 carboxamide, monohydrochloride



Part A: To a solution of the product of
10 Example 429, Part B (1.0 g, 2.9 mmol) in N,N-
dimethylacetamide (30 mL) were added 4-
(trifluoromethyl)benzyl alcohol (1.53 g, 8.74 mmol)
and cesium carbonate (2.85 g, 8.74 mmol), and the
resulting suspension was heated at 95-100 degrees
15 Celsius for 8 hours. The reaction mixture was then
concentrated in vacuo. The residue was dissolved in
ethyl acetate and washed with 1 N sodium hydroxide,
water and brine. Concentration of the organic phase
gave a residue that was purified by chromatography on
20 silica gel eluting with ethyl acetate/hexane to
afford the desired aryl ether (0.8 grams, 54%).

Part B: To a solution of the ethyl ester
of part A (0.8 g, 1.5 mmol) in ethanol (50 mL) and
water (50 mL) was added sodium hydroxide (1.0 g, 25
25 mmol) and the mixture was heated to 60 degrees
Celsius for 16 hours. The solvents were removed in
vacuo. Water (50 mL) was added and the mixture was
acidified with 2 N HCl to pH=4. The solid

-699-

precipitate was collected by filtration to afford the desired carboxylic acid (0.75 g, 99%).

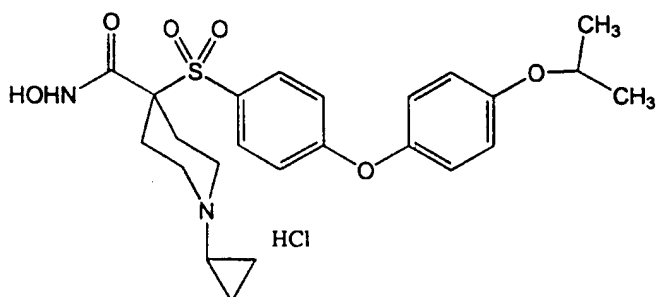
Part C: To a solution of the carboxylic acid of part B (0.75 g, 1.54 mmol) in N,N-dimethylformamide (10 mL) were added 4-methylmorpholine (0.47 g, 4.6 mmol), N-hydroxybenzotriazole (0.25 g, 1.85 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.41 g, 2.16 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.35, 2.3 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (250 mg, 57%).

Part D: To a solution of the protected hydroxamate of part C (250 mg, 0.43 mmol) in methanol/1,4-dioxane (1:3, 20 mL) was added 4 N HCl/1,4-dioxane (5 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed *in vacuo*. An additional portion of ethyl acetate was added and then removed *in vacuo*. Diethyl ether (100 mL) was added and the resulting solid was collected by filtration to afford the title compound (190 mg, 82%). MS (CI) MH^+ calculated for $C_{22}H_{25}F_3N_2O_5S$: 487, found 487.

-700-

Example 439: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]-phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride

5



Part A: To a solution of the product of Example 398, Part A (2.49 g, 7.0 mmol) in N,N-dimethylacetamide (30 mL) were added 4-isopropoxyphenol, which may be prepared according to the procedure of *J. Indian Chem. Soc.* 73, 1996, 507-511, (1.28 g, 8.4 mmol) and cesium carbonate (5.48 g, 16.8 mmol), and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired aryl ether (2.8 grams, 82%).

Part B: To a solution of the ethyl ester of part A (2.8 g, 5.7 mmol) in ethanol (50 mL) and water (50 mL) was added sodium hydroxide (2.3 g, 57 mmol) and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed in

-701-

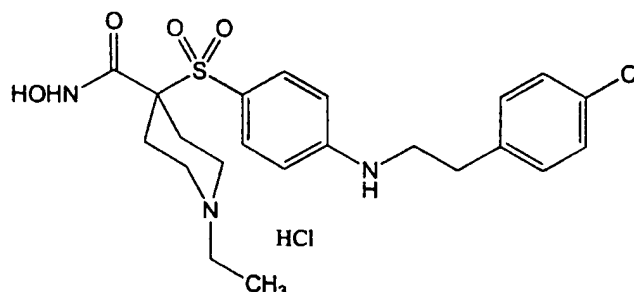
vacuo. Water (50 mL) was added and the mixture was acidified with 2 N HCl to pH = 4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (1.4 g, 53%).

5 Part C: To a solution of the carboxylic acid of part B (1.4 g, 3.1 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.92 g, 9.1 mmol), N-hydroxybenzotriazole (0.49 g, 3.66 mmol), and 1-[3-
10 (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.82 g, 4.26 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.68 g, 4.5 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to
15 a residue that was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the
20 next step.

 Part D: To a solution of the protected hydroxamate from part C in methanol/1,4-dioxane (1:3, 20 mL) was added 4 N HCl/1,4-dioxane (10 mL) and the solution was stirred at ambient temperature for 3
25 hours. The solvent was then removed in vacuo. An additional portion of ethyl acetate was added and then removed in vacuo. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (0.3 g, 19% for parts C and
30 D together). Analytical calculation for $C_{24}H_{30}N_2O_6S \cdot HCl$: C, 56.41; H, 6.11; N, 5.48. Found: C, 56.04; H, 5.82; N, 5.44. MS (CI) MH^+ calculated for $C_{24}H_{30}N_2O_6S$: 475, found 475.

-702-

Example 440: Preparation of 4-[[4-[[2-(4-chlorophenyl)-ethyl]amino]phenyl]-sulfonyl]-1-ethyl-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the product of Example 429, Part B (1.0 g, 2.91 mmol) in N,N-dimethylacetamide (20 mL) were added 4-chlorophenethylamine (0.91 g, 5.8 mmol) and cesium carbonate (3.80 g, 11.6 mmol), and the resulting suspension was heated at 90 degrees Celsius for 24 hours. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/hexane to afford the desired aryl ether (0.8 grams, 58%).

Part B: To a solution of the ethyl ester of part A (0.8 g, 1.7 mmol) in ethanol (50 mL) and water (50 mL) was added sodium hydroxide (1.0 g, 25 mmol), and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed in vacuo. Water (50 mL) was added and the mixture was

-703-

acidified with 2 N HCl to pH=4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (0.75 g, 92%).

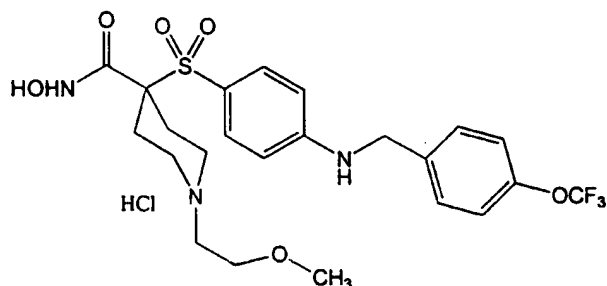
Part C: To a solution of the carboxylic acid of part B (0.75 g, 1.7 mmol) in N,N-dimethylformamide (20 mL) were added 4-methylmorpholine (0.51 g, 5.1 mmol), N-hydroxybenzotriazole (0.27 g, 2.0 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.45 g, 2.3 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.37 g, 2.5 mmol). After stirring for 16 hours at ambient temperature the reaction mixture was concentrated to a residue which was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative which was used directly in the next step.

Part D: To a solution of the protected hydroxamate from part C in methanol/1,4-dioxane was added 4 N HCl/1,4-dioxane (10 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was then removed in vacuo. An additional portion of ethyl acetate was added and then removed in vacuo. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (30 mg, 4% for parts C and D together).

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Example 441 Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[[[4-(trifluoromethoxy)phenyl]methyl]amino]phenyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride

5



Part A: To a solution of ethyl-4-[(4-fluorophenylsulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (1.38g, 3.7 mmol) in N,N-dimethylformamide (20 mL) were added 4-(trifluoromethoxy)benzylamine (1.0 g, 5.2 mmol) and cesium carbonate (1.7 g, 5.2 mmol), and the resulting suspension was heated at 90 degrees Celsius for 24 hours. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired trifluoromethoxy compound (0.6 grams, 30%).

Part B: To a solution of the ethyl ester of part A (0.6 g, 1.1 mmol) in ethanol (30 mL), water (30 mL) and tetrahydrofuran (15 mL) was added sodium hydroxide (0.44 g, 11 mmol), and the mixture was heated to 60 degrees Celsius for 16 hours. The solvents were removed in vacuo. Water (50 mL) was

-705-

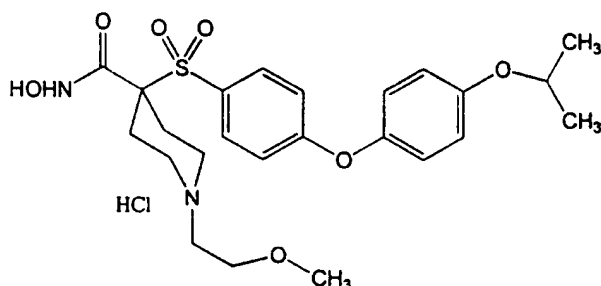
added and the mixture was acidified with 2 N HCl to pH=4. The solid precipitate was collected by filtration to afford the desired carboxylic acid (0.5 g, 88%).

5 Part C: To a solution of the carboxylic acid of part B (0.50 g, 0.98 mmol) in N,N-dimethylformamide (10 mL) were added 4-methylmorpholine (0.15 g, 1.5 mmol), N-hydroxybenzotriazole (0.16 g, 1.2 mmol), and 1-[3-
10 (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.27 g, 1.4 mmol) followed by O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.22 g, 1.5 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to
15 a residue that was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (110 mg, 18%).

20 Part D: To a solution of the protected hydroxamate from part C (110 mg, 0.18 mmol) in methanol/1,4-dioxane (1:4, 20 mL) was added 4 N HCl/1,4-dioxane (7 mL) and the solution was stirred at ambient temperature for 3 hours. The solvent was
25 then removed *in vacuo*. An additional portion of methanol (20 mL) was added and then removed *in vacuo*. Diethyl ether was added and the resulting solid was collected by filtration to afford the title compound (30 mg, 31%). MS (ESI) MH^+ calculated for
30 $C_{23}H_{28}F_3N_3O_6S$: 532, found 532.

-706-

Example 442: Preparation of N-hydroxy-4-[[4-[4-(1-methylethoxy)phenoxy]phenyl]sulfonyl]-1-(2-methoxyethyl)-4-piperidinecarboxamide,
5 monohydrochloride



Part A: To a solution of ethyl-4-[(4-fluorophenyl-sulfonyl)]-1-(2-methoxyethyl)-4-piperidinecarboxylate (2.0 g, 5.4 mmol) in N,N-dimethylformamide (20 mL) were added 4-isopropoxyphenol, which can be prepared according to the procedure of *J. Indian Chem. Soc.* **73**, 1996, 507-511, (1.63 g, 10.7 mmol) and cesium carbonate (7 g, 21.5 mmol), and the resulting suspension was heated at 60 degrees Celsius for 16 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, water and brine and dried over magnesium sulfate. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel, eluting with ethyl acetate/hexane, to afford the desired aryl ether (1.37 grams, 50%).

Part B: To a solution of the ethyl ester of part A (1.37 g, 2.7 mmol) in ethanol (30 mL) and water (30 mL) was added sodium hydroxide (1.08 g, 27

-707-

mmol), and the mixture was heated to 65 degrees Celsius for 16 hours. The solvents were then removed in vacuo. Water (50 mL) was added and the mixture was again concentrated in vacuo and the resulting
5 mixture was acidified with 2 N HCl to pH = 4-5. The solid precipitate was collected by filtration and rinsed with diethyl ether to afford the desired carboxylic acid (1.25 g, 100%).

Part C: To a suspension of the carboxylic
10 acid of part B (1.25 g, 2.7 mmol) in N,N-dimethylformamide (15 mL) were added 4-methylmorpholine (0.82 g, 8.1 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.61, 4.1 mmol) followed by bromo-tris-pyrrolidino-phosphonium
15 hexafluorophosphate (PyBroP, 1.51 g, 3.3 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in ethyl acetate and washed with water and brine. Concentration and purification by
20 chromatography on silica, gel eluting with ethyl acetate/hexane, afforded the protected hydroxamate derivative (1.0 g, 63%).

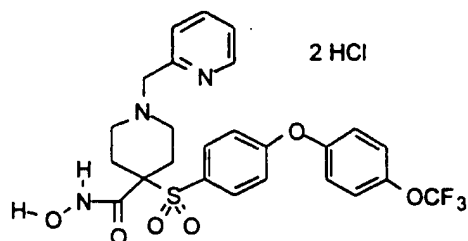
Part D: Hydrogen chloride gas was bubbled for 5 minutes through an ice bath-cooled solution of
25 the protected hydroxamate of part C (1.0 g, 1.7 mmol) in ethyl acetate (20 mL). After stirring at ambient temperature for 5 hours, the solvent was removed in vacuo. Ethyl acetate (30 mL) was added and then removed in vacuo. Ethyl acetate (30 mL) was again
30 added and the resulting solid was collected by filtration to afford the title compound (0.5 g, 56%). Analytical calculation for $C_{24}H_{32}N_2O_7S \cdot HCl \cdot 1.5H_2O$: C, 51.84; H, 6.53; N, 5.04; Cl, 6.38; S, 5.77. Found:

-708-

C, 51.87; H, 6.12; N, 4.92; Cl, 6.38; S, 5.84. MS MH^+ calculated for $C_{24}H_{32}N_2O_7S$: 493, found 493.

5 Example 443: Preparation of N-Hydroxy-1-(2-pyridinylmethyl)-4-[4-(4-trifluoromethoxyphenoxy)phenyl]sulfonyl]-4-piperidinecarboxamide, dihydrochloride

10



Part A: The aryl fluoride from Example 9, Part D (6.22 g, 15 mmol) was combined with powdered potassium carbonate (3.04 g, 22 mmol), 4-(trifluoromethoxy)phenol (3.92 g, 322 mmol), and N,N-dimethylformamide (7 mL), and the mixture was stirred at ninety degrees Celcius for sixteen hours. Additional 4-(trifluoromethoxy)-phenol (1 g) and potassium carbonate (800 mg) were added and the reaction was continued at one hundred and fifteen degrees Celsius for twenty additional hours. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL, then 2 X 25 mL). The combined organic layers were dried using magnesium sulfate, concentrated, and chromatographed, affording the desired aryl ether as an oil (9.6 g, about quantitative).

Part B: The aryl ether from part A (9.6 g, about 15 mmol) was dissolved in ethyl acetate (45

-709-

mL). A solution of HCl in dioxane (4N, 12 mL) was added, and the mixture was stirred at ambient temperature for three hours. Thin layer chromatography indicated incomplete deprotection.

- 5 Concentrated aqueous HCl (4 mL) was added and the reaction was heated to reflux with a heat gun several azeotropes with acetonitrile to afford the desired piperidine hydrochloride salt as a foam (9.6 g).
- 10 Nuclear magnetic resonance spectroscopy indicated some contaminating 4-(trifluoromethoxy)phenol, which must have been carried through from part A.

- The piperidine hydrochloride salt (6.0 g) was dissolved in ethyl acetate (125 mL) and washed
- 15 with aqueous sodium hydroxide (2 g NaOH in 50 mL water). The organic layer was dried with magnesium sulfate and filtered through a pad of silica gel. The phenol contaminant was eluted. The desired piperidine was then freed from the filter cake by
- 20 elution with methanol containing 1% aqueous ammonium hydroxide (circa 100 mL). The filtrate was concentrated and azeotroped with acetonitrile to yield 3.3 g (7.3 mmol).

- Part C: The piperidine from Part B (1.24 g,
- 25 2.7 mmol) was combined with powdered potassium carbonate (828 mg, 6.0 mmol), 2-picoly hydrochloride (492 mg, 3.0 mmol), and N,N-dimethylformamide (3 mL), and the mixture was stirred at ambient temperature for two hours, then heated at fifty degrees Celsius
- 30 for two additional hours. The mixture was diluted with water (40 mL) and extracted with ethyl acetate (150 mL, then 50 mL). The combined organic layers were dried using magnesium sulfate, concentrated, and

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chromatographed, affording the desired ester as an oil (1.13 g, 74%).

Part D: The ester from part C (1.1 g, 2.0 mmol) was combined with ethanol (6 mL), water (2 mL), and potassium hydroxide (0.90 g, 16 mmol). The mixture was brought to reflux and heated for four and one-half hours. The solution was then cooled to zero degrees Celsius and acidified using concentrated aqueous hydrogen chloride. The solvent was removed, and the resulting solids were dried by azeotroping with acetonitrile. A vacuum was applied until constant weight was achieved.

The crude acid hydrochloride salt was stirred with N-methylmorpholine (about 0.5 mL), 1-hydroxybenzotriazole (0.405 g, 3 mmol), O-tetrahydropyranyl hydroxylamine (0.35 g, 3.0 mmol), and N,N-dimethylformamide (9 mL). After ten minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.57 g, 3.0 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous sodium bicarbonate (50 mL), and extracted with ethyl acetate (100 mL, then 25 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed (9:1 ethyl acetate: methanol) to afford the desired tetrahydropyranyl-protected hydroxamate as a yellow oil (1.20 g, 95%).

Part E: The tetrahydropyranyl-protected hydroxamate (1.20 g, 1.90 mmol) was diluted with methanol (9 mL). Acetyl chloride (0.78 mL, 11 mmol) was added over two minutes. The reaction was stirred for 2 hours at ambient temperature, then concentrated to afford the desired dihydrochloride salt (1.20 g,

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quantitative yield) as a white crystalline solid. Analytical calculation for $C_{25}H_{24}F_3N_3O_6S \cdot 2HCl \cdot 1/3 H_2O$: C, 47.58; H, 4.07; N, 6.66. Found: C, 47.31; H, 4.14; N, 6.80.

5

Example 444: In Vitro Metalloprotease Inhibition

The compounds prepared in the manner described in the Examples above were assayed for activity by an in vitro assay. Following the
10 procedures of Knight et al., *FEBS Lett.* 296(3):263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin-activated MMPs were incubated with various concentrations of the inhibitor compound at room temperature for 5 minutes.

15

More specifically, recombinant human MMP-13, MMP-1, MMP-2 and MMP-9 enzymes were prepared in laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a
20 baculovirus as discussed in V.A. Luckow, *Insect Cell Expression Technology*, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, 67:4566-4579 (1993); O'Reilly et
25 al., Baculovirus Expression Vectors: A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al., The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992) for further details on use of baculovirus expression
30 systems. The expressed enzyme was purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay.

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MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr. Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Further specifics for preparation and use of these enzymes can be found in the scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, Ca (1992) and the citations therein, and Frije et al., J. Biol. Chem., 26(24): 16766-16773 (1994). The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

MCA-ProLeuGlyLeuDpaAlaArgNH₂, wherein MCA is methoxycoumarin and Dpa is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine. This substrate is commercially available from Baychem as product M-1895.

The buffer used for assays contained 100 mM Tris-HCl, 100 mM NaCl, 10 mM CaCl₂ and 0.05 percent polyethyleneglycol (23) lauryl ether at a pH value of 7.5. Assays were carried out at room temperature, and dimethyl sulfoxide (DMSO) at a final concentration of 1 percent was used to dissolve inhibitor compound.

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The assayed inhibitor compound in DMSO/buffer solution was compared to an equal amount of DMSO/buffer with no inhibitor as control using Microfluor™ White Plates (Dynatech). The inhibitor or control solution was maintained in the plate for 10 minutes and the substrate was added to provide a final concentration of 4 μ M.

In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the gly-leu peptide bond, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescence intensity (excitation at 328 nm/emission at 415 nm). Inhibition was measured as a reduction in fluorescent intensity as a function of inhibitor concentration, using a Perkin Elmer L550 plate reader. The IC₅₀ values were calculated from those values. The results are set forth in the Inhibition Tables A and B below, reported in terms of IC₅₀ to three significant figures, where appropriate.

Inhibition Table A (nM)

Example Number	MMP-13 IC ₅₀ (nM)	MMP-2 IC ₅₀ (nM)	MMP-1 IC ₅₀ (nM)	MMP-9 IC ₅₀ (nM)
1	5.1	2.6	6600	31.6
2	0.25	0.1	220	1.4
3	0.3	0.2	1140	
4	0.35	0.23	1090	5
5	4800	1800	>10000	
6	0.25	0.15	327	
7	37.2	1.8	>10000	235

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8	24.1	4	>10000	290
9	0.5	0.2	9000	1.5
10	0.4	0.2	1600	0.3
11	6	4.4	>10000	
12	<0.1	<0.1	464	
13	0.6	0.4	>10000	8
14	0.1	<0.1	464	
15	0.4	0.2	3600	0.2
16	2.4	100	>10000	2500
17	0.3	0.2	400	0.3
18	0.5	0.3	800	
19	9	13.9	>10000	
20	1.7	23.5	10000	
21	0.6	1.3	>10000	
22	1.2	0.9	>10000	
23	0.2	<0.1	2275	
24	0.4	1	>10000	3.7
25	3	2.6	>10000	
26	0.5	0.2	7700	7
27	0.45	0.4	>10000	4
28	<0.1	<0.1	770	
29	0.3	0.15	>10,000	

Inhibition Table B (nM)

Example Number	MMP-1 IC ₅₀ (nM)	MMP-2 IC ₅₀ (nM)	MMP-9 IC ₅₀ (nM)	MMP-13 IC ₅₀ (nM)
30	350	0.1	0.3	0.1
31	370	<0.1		0.2
32	>10000	0.1	2.5	0.2
33	>10000	0.5	9.4	0.8

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34	>10000	1.1		1.2
35	>10000	0.3	3	0.5
36	7300	0.4	8	0.6
37	1000	0.2		0.3
38	>10000	20	135	22
39	>10000	230		24.5
40	4400	0.4	2.4	1.9
41	1200	0.15		0.2
42	2200	0.2	1.3	0.4
43	7000	0.4		0.8
44a	>10000	<0.1		0.2
44b	>10000	8000		>10000
45	8800	2.5		1.7
46	710000	—	—	710000
47a	>10000	7		14.6
47b	>10000	3000		3100
48	210	0.2		0.25
49	>10000	76.9		90.0
51	5500	0.7		1.3
52	>10000	2.7		5.9
53	>10000	0.3	92	1.5
54	>10000	60		120
55	1200	0.1		0.3
56	1500	<0.1		0.15
57	1200	<0.1		0.2
58	>10000	83		30
59	>10000	130		180
60	>10000	64		147
61	>10000	1500		2000
62	>10000	>10000		>10000
63	>10000	18.1	530	1.5
64	1470	<0.1		0.15

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65	8000	0.6	4.4	0.7
66	>10000	4590		36000
67	1600	239		268
68	>10000	5.3	130	6
69	1140	<0.1	0.2	<0.1
70	1500	0.2	7.3	0.8
71	3600	0.35	5	0.8
72	2100	<0.1		0.3
73	1140	<0.1	0.2	<0.1
74	>10000	130		480
75	>10000	60		900
78	>10000	6	50	10
79	>10000	1		1.7
80	3000	0.1	1.8	0.2
81	3300	0.1		0.3
82	4000	0.1		0.3
83	8000	1.2	5	1.5
84	8000	1.8		2.5
85	500	<0.1	0.4	<0.1
86	>10000	2.5		3.5
87	7200	0.8	13.9	0.35
88	1100	0.2	0.5	0.2
89	1200	0.15	0.4	0.25
90	1200	0.1		0.1
91	1800	1.5	40	2.1
92	>10000	1800		2430
93	8000	0.4	3.5	0.7
94	268	<0.1	0.4	<0.1
95	>10000	1	3.6	0.5
96	5000	0.2	1.3	0.3
97	4000	8.2		16.7
98	>10000	37		23.4

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99	>10000	0.4		1
100	435	<0.1	0.3	0.15
101	1800	0.3	2.9	0.45
102	2000	<0.1		0.2
103	>10000	0.8	10	0.7
104	>10000	1.5	42.8	0.65
105	>10000	3500	114	0.85
106	>10000	27.1		12.1
107	>10000	12.1		6
108	2000	0.4		0.4
109	500	0.1	0.7	0.3
110	2700	0.4	10	0.5
111	3700	0.5		1.3
112	1000	7		3.2
113	>10000	0.9		4
114	3000	0.65	31.6	0.4
115	4500	0.3	31.6	0.6
116	2350	2	15.3	5.5
117	3700	0.6	45.4	4.8
118	2850	0.3	50	0.8
119	>10000	1.5	30	1.7
120	4000	0.4		0.4
121	1200	<0.1		0.2
122	600	0.1		0.15
123	3600	1.8	27.8	1.8
124	1000	0.5		1.1
125	>10000	0.4	7	0.5
126	8000	11.3		10
127	>10000	37		40
128	>10000	23.8		20
129	>10000	>100		1000
130	>10000	57.7		45.9

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131	>10000	650	10
132	>10000	420	
133	>10000	90	27
134	9000	29	4
135	>10000	500	65
136	>10000	445	40
137	>10000	300	34.7
138	>10000	>100	>100
139	>10000	1000	25.4
140	>10000	1000	60
141	>10000	>100	>100
142	>10000	600	70
143	>10000	900	23.9
144	>10000	800	30.7
145	>10000	>100	>100
146	>10000	650	32.6
147	>10000	2700	31
148	>10000	2400	31
149	>10000	1600	15.5
150	>10000	1300	14.5
151	>10000	1500	35
152	>10000	2400	16.5
153	>10000	2700	13.5
154	>10000	1600	27
155	>10000	>1000	>100
156	>10000	3300	27.8
157	>10000	6000	90
158	>10000	5000	80
159	>10000	2500	15.6
160	>10000	4700	33.7
161	>10000	>1000	>100
162	>10000	>1000	>100

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163	>10000	4000	77.4
164	>10000	1750	20
165	>10000	330	13.6
166	>10000	>1000	>100
167	>10000	>1000	>100
168	>10000	>1000	>100
169	10000	>1000	>100
170	10000	>1000	>100
171	>10000	>1000	>100
172	>10000	>1000	>100
173	>10000	>1000	>100
174	8000	900	>100
175	10000	>1000	>100
176	>10000	400	25
177	>10000	400	21
178	>10000	540	>100
179	>10000	440	100
180	5000	128	4
181	10000	121	6.1
182	>10000	240	4
183	>10000	288	40
184	>10000	94	7
185	>10000	210	17.5
186	>10000	120	10
187	>10000	290	12.1
188	>10000	350	9.4
189	3700	94	8
190	>10000	220	10.6
191	>10000	350	4
192	>10000	330	10
193	>10000	390	6
194	10000	165	8

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195	10000	100	14.5
196	>10000	240	25
197	7000	145	8
198	>10000	270	14.5
199	>10000	155	1.4
200	>10000	24	17.5
201	>10000	22.4	13.6
202	>10000	54	9.15
203	8500	31	30
204	>10000	25	27.1
205	7300	12.7	2
206	>10000	>10.0	20
207	>10000	30.6	28
208	>10000	27	27
209	>10000	19	20
210	>10000	27	20
211	>10000	33	24
212	>10000	33	20
213	310	<1.0	<1.0
214	1100	<1.0	<1.0
215	250	<1.0	<1.0
216	1000	<1	<1.0
217	600	<1.0	<1.0
218	>10000	<1.0	<1.0
219	>10000	<1.0	<1.0
220	145	<1.0	<1.0
221	1600	<1.0	<1.0
222	100	<1.0	<1.0
223	1100	<1.0	<1.0
224	>10000	18.1	16.7
225	>10000	54	70
226	>10000	18.6	6

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227	>10000	<1	<1
228	600	<1.0	<1.0
229	>10000	<1	<1
230	>10000	>100	>100
231	650	<1.0	<1.0
232	<100	<1.0	<1.0

Example 445: In Vivo Angiogenesis Assay

The study of angiogenesis depends on a
 5 reliable and reproducible model for the stimulation
 and inhibition of a neovascular response. The
 corneal micropocket assay provides such a model of
 angiogenesis in the cornea of a mouse. See, *A Model*
of Angiogenesis in the Mouse Cornea; Kenyon, BM,
 10 et al., *Investigative Ophthalmology & Visual Science*,
 July 1996, Vol. 37, No. 8.

In this assay, uniformly sized Hydron™
 pellets containing bFGF and sucralfate were prepared
 and surgically implanted into the stroma mouse cornea
 15 adjacent to the temporal limbus. The pellets were
 formed by making a suspension of 20 µL sterile saline
 containing 10 µg recombinant bFGF, 10 mg of
 sucralfate and 10 µL of 12 percent Hydron™ in
 ethanol. The slurry was then deposited on a 10 x 10
 20 mm piece of sterile nylon mesh. After drying, the
 nylon fibers of the mesh were separated to release
 the pellets.

The corneal pocket is made by anesthetizing
 a 7 week old C57Bl/6 female mouse, then proptosing
 25 the eye with a jeweler's forceps. Using a dissecting
 microscope, a central, intrastromal linear keratotomy

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of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet was placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet was then advanced to the temporal end of the pocket.

Antibiotic ointment was then applied to the eye.

Mice were dosed on a daily basis for the duration of the assay. Dosing of the animals was based on bioavailability and overall potency of the compound. an exemplary dose was 10 or 50 mg/kg (mpk) bid, po. Neovascularization of the corneal stroma begins at about day three and was permitted to continue under the influence of the assayed compound until day five. At day five, the degree of angiogenic inhibition was scored by viewing the neovascular progression with a slit lamp microscope.

The mice were anesthetized and the studied eye was once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet was measured. In addition, the contiguous circumferential zone of neovascularization was measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis was calculated as follows.

30

$$\text{area} = \frac{(0.4 \times \text{clock hours} \times 3.14 \times \text{vessel length (in mm)})}{2}$$

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Five to six mice were utilized for each compound in each study. The studied mice were thereafter compared to control mice and the difference in the area of neovascularization was recorded as an averaged value. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

Data for four compounds of the above examples are provided below at dosages of 10 and 50 mpk.

Inhibition of Angiogenesis

20

<u>Example</u>	<u>Dosage</u>	
	<u>10 mpk</u>	<u>50 mpk</u>
Marimastat	--	48 (n=6)
25 4	18 (n=3)	41 (n=6)
9	50 (n=2)	46 (n=3)
10	47 (n=1)	54 (n=2)
24	53 (n=1)	78 (n=1)

30

Example 446: In Vivo PC-3 Tumor Reduction

PC-3 human pancreatic cancer cells (ATCC CRL 1435) were grown to 90% confluence in F12/MEM

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(Gibco) containing 7% FBS (Gibco). Cells were mechanically harvested using a rubber scraper, and then washed twice with cold medium. The resulting cells were resuspended in cold medium with 30% matrigel (Collaborative Research) and the cell-containing medium was maintained on ice until used.

Balb/c nu/nu mice at 7-9 weeks of age were anesthetized with avertin [2,2,2-tribromethanol/t-amyl alcohol (1 g/1 mL) diluted 1:60 into phosphate-buffered saline] and $3-5 \times 10^6$ of the above cells in 0.2 mL of medium were injected into the left flank of each mouse. Cells were injected in the morning, whereas dosing with an inhibitor began at 6 PM. The animals were gavaged BID from day zero (cell injection day) to day 25-30, at which time the animals were euthanized and tumors weighed.

Compounds were dosed at 10 mg/mL in 0.5% methylcellulose/0.1% polysorbate 80 to provide a 50 mg/kg (mpk) dose twice each day, or diluted to provide a 10 mg/kg (mpk) dose twice each day. Tumor measurements began on day 7 and continued every third or fourth day until completion of the study. Groups of ten mice were used in each study and nine to ten survived. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. The results of this study for several of the before discussed compounds are shown below as average reductions in tumor weight.

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Average Percentage Reduction
In Tumor Weight

		<u>Dosage</u>	
		<u>10 mpk</u>	<u>50 mpk</u>
5	<u>Example</u>		
	Marimastat	<5	39 (n=2)
	4	33 (n=2)	43 (n=2)
	9	40 (n=1)	60 (n=1)
	10	nt	59 (n=1)

10

Example 447: Tumor Necrosis Factor Assays

Cell Culture.

15

The cells used in the assay are the human monocytic line U-937 (ATCC CRL-1593). The cells are grown in RPMI w/10% FCS and PSG supplement (R-10) and are not permitted to overgrow. The assay is carried out as follows:

20

1. Count, then harvest cells by centrifugation. Resuspend the pellet in R-10 supplement to a concentration of 1.540×10^6 cells/mL.

25

2. Add test compound in 65 uL R-10 to the appropriate wells of a 96-well flat bottom tissue culture plate. The initial dilution from a DMSO stock (100 mM compound) provides a 400 uM solution, from which five additional three-fold serial dilutions are made. Each dilution of 65 ul (in triplicate) yields final compound test concentrations of 100 μ M, 33.3 μ M, 11.1 μ M, 3.7 μ M, 1.2 μ M and 0.4 μ M.

30

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3. The counted, washed and resuspended cells (200,000 cells/well) in 130 μ L are added to the wells.

4. Incubation is for 45 minutes to one hour at 37°C in 5% CO₂ in a water saturated container.

5. R-10 (65 μ L) containing 160 ng/mL PMA (Sigma) is added to each well.

6. The test system is incubated at 37°C in 5% CO₂ overnight (18-20 hours) under 100% humidity.

7. Supernatant, 150 μ L, is carefully removed from each well for use in the ELISA assay.

8. For toxicity, a 50 μ L aliquot of working solution containing 5 mL R-10, 5 mL MTS solution [CellTiter 96 Aqueous One Solution Cell Proliferation Assay Cat.#G358/0,1 (Promega Biotech)] and 250 μ L PMS solution are added to each well containing the remaining supernatant and cells and the cells incubated at 37°C in 5% CO₂ until the color develops. The system is excited at 570 nm and read at 630 nm.

20

TNF Receptor II ELISA Assay

1. Plate 100 μ L/well 2 μ g/mL mouse anti-human TNFrII antibody (R&D Systems #MAB226) in 1 x PBS (pH 7.1, Gibco) on NUNC-Immuno Maxisorb plate.

25 Incubate the plate at 4°C overnight (about 18-20 hours).

2. Wash the plate with PBS-Tween (1 x PBS w/ 0.05% Tween).

3. Add 200 μ L 5% BSA in PBS and block at 37°C in a water saturated atmosphere for 2 hours.

30

4. Wash the plate with PBS-Tween.

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5. Add sample and controls (100 μ L of each) to each well. The standards are 0, 50, 100, 200, 300 and 500 pg recombinant human TNFrII (R&D Systems #226-B2) in 100 μ L 0.5% BSA in PBS. The assay is

5 linear to between 400-500 pg of standard.

6. Incubate at 37°C in a saturated atmosphere for 1.5 hours.

7. Wash the plate with PBS-Tween.

8. Add 100 μ L goat anti-human TNFrII

10 polyclonal (1.5 μ g/mL R&D Systems #AB226-PB in 0.5% BSA in PBS).

9. Incubate at 37°C in a saturated atmosphere for 1 hour.

10. Wash the plate with PBS-Tween.

15 11. Add 100 μ L anti-goat IgG-peroxidase (1:50,000 in 0.5% BSA in PBS, Sigma #A5420).

11. Incubate at 37°C in a saturated atmosphere for 1 hour.

12. Wash the plate with PBS-Tween.

20 13. Add 10 μ L KPL TMB developer, develop at room temperature (usually about 10 minutes), then terminate with phosphoric acid and excite at 450 nm and read at 570 nm.

25 TNF α ELISA Assay

Coat Immulon[®] 2 plates with 0.1 mL/well of 1 μ g/mL Genzyme mAb in 0.1 M NaHCO₃ pH 8.0 buffer overnight (about 18-20 hours) at 4°C, wrapped tightly in Saran[®] wrap.

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Flick out coating solution and block plates with 0.3 mL/well blocking buffer overnight at 4°C, wrapped in Saran[®] wrap.

Wash wells thoroughly 4X with wash buffer
5 and completely remove all wash buffer. Add 0.1 mL/well of either samples or rhTNF α standards. Dilute samples if necessary in appropriate diluant (e.g. tissue culture medium). Dilute standard in same diluant. Standards and samples should be in
10 triplicates.

Incubate at 37°C for 1 hour in humified container.

Wash plates as above. Add 0.1 mL/well of 1:200 dilution of Genzyme rabbit anti-hTNF .

15 Repeat incubation.

Repeat wash. Add 0.1 mL/well of 1 μ g/mL Jackson goat anti-rabbit IgG (H+L)-peroxidase.

Incubate at 37°C for 30 minutes.

Repeat wash. Add 0.1 mL/well of peroxide-
20 ABTS solution.

Incubate at room temperature for 5-20 minutes.

Read OD at 405 nm.

25 12 Reagents are:

Genzyme mouse anti-human TNF α monoclonal (Cat.# 80-3399-01)

Genzyme rabbit anti-human TNF α polyclonal (Cat.#IP-300)

30 Genzyme recombinant human TNF α (Cat.#TNF-H).

Jackson ImmunoResearch peroxide-conjugated goat anti-rabbit IgG (H+L) (Cat.#111-035-144).

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Kirkegaard/Perry peroxide ABTS solution
(Cat#50-66-01).

Immulon 2 96-well microtiter plates.

Blocking solution is 1 mg/mL gelatin in PBS
5 with 1X thimerasol.

Wash buffer is 0.5 mL Tween[®] 20 in 1 liter
of PBS.

Results:

10

Example Number	MTS Toxicity TD ₅₀ in micromolar	TNFR II Release IC ₅₀ in micromolar	TNF α Release IC ₅₀ in micromolar
DMSO	>100	>100	>100
4	>100	>100	>50
6	>100	>100	>50
9	>100	>100	>50
10	>100	>100	>50
13	>100	>100	>50
27	100	>100	>80
35	>100	>100	>80
69	100	>100	>80
95	>100	>100	>50
379	80	>100	80

Example 448: Pharmacokinetic (PK)-evaluation of MMP
inhibitors in rats

15

Under metofane anesthesia, the femoral
artery (all 8 rats) and femoral vein (only 4 of 8
rats) are isolated and canulated with PE50 tubing and
secured with 3.0 silk suture. The following
20 determinations require two catheters, with the venous
line being used for infusion of compound (in the
group of rats that receives compound via the
intravenous (IV) route.), and the arterial line being
used for collection of blood samples. The rats are

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then placed in restraining cages that permit minimal movement and allowed to recover from anesthesia for approximately 30 minutes. At time 0 (prior to dosing), blood samples (400 μ L) are collected from
5 arterial cannula.

One group of rats (4 rats per group) receives compound via the oral route at a dosing volume of 2 mL/kg (10mg/mL, dissolved in 0.5% methylcellulose, 0.1% Tween[®] 20), while the other
10 group of rats receives compound via the intravenous cannula, at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 10% EtOH, 50% PEG 400, 40% saline). The blood samples are collected from the arterial cannula at 15, 30, 60, 120, 240, and 360 minutes from the
15 oral group with an additional 3 minute sample being collected from IV group. After each sample, the cannulas are flushed with PBS containing 10 units/mL heparin. The animals are subjected to euthanasia with an excess of anesthesia or carbon monoxide
20 asphyxiation when the study is terminated at 6 hours. Blood samples from each time point are assayed for MMP-13 enzyme inhibitory activity and the circulating concentration of compound plus active metabolites is estimated based on the standard curve.

25 Pharmacokinetic (PK) parameters are calculated by the VAX computer program CSTRIP. The parameters are defined in textbooks such as *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, eighth ed., McGraw-Hill, Inc., New York (1993) and the references
30 therein.

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Example Number	Rat Intravenous			Rat Oral			
	20 mpk			20 mpk			
	$t_{1/2}$	AUC (0- ∞)	Blood Level @ 3 min	Cmax	AUC (0-6 hr)	BA	Blood Level @ 6 hr
	Hour	hr* μ g/ mL	μ g/mL	μ g/mL	hr* μ g/mL	%	μ g/mL
4	1.77	24.80	37.60	1.84	4.14	16.7	0.254
6	1.19	46.39	84.72	22.88	16.45	35.5	0.345
9	1.10	33.67	42.17	13.63	9.43	28.0	0.281
10	0.84	43.01	73.00	18.47	12.93	30.1	0.134
12	0.86	22.11	73.54	1.00	2.45	11.1	0.121
13	1.03	43.08	91.07	21.98	18.08	42.0	0.228
14	1.25	12.92	12.10	4.13	7.66	59.3	0.102
15	1.01	49.29	120.83	27.16	18.19	36.9	0.192
17	0.74	37.10	63.44	15.72	13.32	35.9	0.135
22	1.47	14.05	18.06	0.82	1.82	13.0	0.174
23	0.85	25.01	59.92	7.31	5.93	23.7	0.087
24	2.49	37.35	62.52	9.79	15.88	42.5	0.545
25	-	-	-	1.48			0.173
26	0.58	17.51	64.01	0.29	0.83	4.7	0.051
27	1.10	43.32	43.69	10.87	21.24	49.0	0.427
28	-	-	-	10.02	24.28		0.537
32	1.03	38.94	51.48	7.65	13.48	34.6	0.529
33	1.91	29.96	24.13	3.33	8.25	27.5	0.543
34	-	-	-	2.13			0.495
35	-	-	-	12.59	26.97		1.237
36	0.65	5.74	19.66	0.16	0.73	12.7	0.072
40	-	-	-	1.55			0.128
42	-	-	-	0.71			0.036
43	0.82	18.79	61.76	4.17	3.24	17.2	0.040
53	0.97	10.78	31.68	0.37	0.48	4.4	BLD
65	-	-	-	0.99			0.080
68	-	-	-	3.41			0.038
69	1.87	63.78	44.00	8.58	22.89	35.9	1.172
70	-	-	-	3.08			0.131
71	-	-	-	4.00			0.452
72	-	-	-	1.42	2.03		0.062
73	-	-	-	1.89	6.87		0.372
79	1.82	6.11	13.99	0.02	0.07	1.1	0.010
80	-	-	40.83	0.03			0.003
81	0.76	38.21	89.01	5.06	6.40	16.7	0.074
89	-	-	-	1.68			0.196
90	-	-	-	0.08			0.041
91	-	-	-	0.17			0.138
93	1.81	13.48	20.88	0.35	1.55	11.5	0.126
94	1.71	25.13	43.37	0.87	1.34	5.3	0.050
95	1.06	19.74	34.71	1.74	4.86	24.6	0.148
96				0.43			0.076
99	0.68	35.68	99.49	14.25	8.05	22.6	0.071
100	1.50	24.60	26.06	3.12	11.30	45.9	0.506
103	1.10	19.66	31.11	2.55	0.09	19.9	0.092
104	0.66	9.86	29.82	9.89	4.88	49.4	0.008
108	-	-	-	2.96			0.108
109	1.12	7.13	13.91	0.93	0.85	11.9	0.027
110			2.67	0.02			0.015

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111	0.65	8.49	33.56	0.45	1.11	13.1	0.054
115	1.36	7.81	12.95	1.17	2.00	25.6	0.058
117	0.78	8.69	40.50	0.18	0.28	3.3	0.016
118	1.85	10.97	17.18	0.75	3.32	30.3	0.266
121	-	-	-	0.31			0.055
123	-	-	-	1.43			0.017
125	0.73	15.73	25.36	1.11	2.50	15.9	0.119
233	0.85	23.12	31.90	3.33	6.22	26.9	0.584
379	1.74	51.41	37.54	4.30	16.80	32.7	1.154
382	1.71	73.68	48.81	7.27	36.12	49.0	3.113
387	-	-	-	0.65			0.558
388	0.94	26.10	34.62	0.15	0.68	2.6	0.073
390	1.50	127.63	120.60	23.21	44.20	34.6	1.780
391	1.45	120.92	82.87	24.02	73.24	60.6	2.680
400			104.34	8.55			0.160
408	3.30	25.18	57.40	9.46	4.17	16.6	0.015
410	1.78	29.83	40.08	0.63	2.08	6.7	0.223
414	0.73	26.15	61.89	5.31	6.22	23.8	0.021
416	2.94	230.70	111.17	29.63	156.71	67.9	20.52
418	2.42	209.92	78.55	20.65	77.52	36.9	7.347
421	-	-	-	13.08	19.21		0.206
427	2.85	36.72	50.74	4.16	8.44	23.0	0.440
437	-	-	-	4.21	4.43		0.128
438	2.14	9.05	7.46	0.39	1.86	20.6	0.316

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Example Number	Rat Intravenous			Rat Oral			
	20 mpk			20 mpk			
	t1/2	AUC (0-∞)	Blood Level @ 3 min	Cmax	AUC (0-6hr)	BA	Blood Level @ 6 hr
	Hour	hr*μg/mL	μg/mL	μg/mL	hr*μg/mL	%	μg/mL
4	1.77	24.80	37.60	1.84	4.14	16.7	0.254
6	1.19	46.39	84.72	22.88	16.45	35.5	0.345
9	1.10	33.67	42.17	13.63	9.43	28.0	0.281
10	0.84	43.01	73.00	18.47	12.93	30.1	0.134
12	0.86	22.11	73.54	1.00	2.45	11.1	0.121
13	1.03	43.08	91.07	21.98	18.08	42.0	0.228
14	1.25	12.92	12.10	4.13	7.66	59.3	0.102
15	1.01	49.29	120.83	27.16	18.19	36.9	0.192
17	0.74	37.10	63.44	15.72	13.32	35.9	0.135
22	1.47	14.05	18.06	0.82	1.82	13.0	0.174
23	0.85	25.01	59.92	7.31	5.93	23.7	0.087
24	2.49	37.35	62.52	9.79	15.88	42.5	0.545
25	-	-	-	1.48			0.173
26	0.58	17.51	64.01	0.29	0.83	4.7	0.051
27	1.10	43.32	43.69	10.87	21.24	49.0	0.427
28	-	-	-	10.02	24.28		0.537
32	1.03	38.94	51.48	7.65	13.48	34.6	0.529
33	1.91	29.96	24.13	3.33	8.25	27.5	0.543
34	-	-	-	2.13			0.495
35	-	-	-	12.59	26.97		1.237
36	0.65	5.74	19.66	0.16	0.73	12.7	0.072
40	-	-	-	1.55			0.128
42	-	-	-	0.71			0.036
43	0.82	18.79	61.76	4.17	3.24	17.2	0.040
53	0.97	10.78	31.68	0.37	0.48	4.4	BLD
65	-	-	-	0.99			0.080
68	-	-	-	3.41			0.038
69	1.87	63.78	44.00	8.58	22.89	35.9	1.172
70	-	-	-	3.08			0.131
71	-	-	-	4.00			0.452
72	-	-	-	1.42	2.03		0.062
73	-	-	-	1.89	6.87		0.372
79	1.82	6.11	13.99	0.02	0.07	1.1	0.010
80	-	-	40.83	0.03			0.003
81	0.76	38.21	89.01	5.06	6.40	16.7	0.074
89	-	-	-	1.68			0.196
90	-	-	-	0.08			0.041
91	-	-	-	0.17			0.138
93	1.81	13.48	20.88	0.35	1.55	11.5	0.126
94	1.71	25.13	43.37	0.87	1.34	5.3	0.050
95	1.06	19.74	34.71	1.74	4.86	24.6	0.148
96				0.43			0.076
99	0.68	35.68	99.49	14.25	8.05	22.6	0.071
100	1.50	24.60	26.06	3.12	11.30	45.9	0.506
103	1.10	19.66	31.11	2.55	0.09	19.9	0.092
104	0.66	9.86	29.82	9.89	4.88	49.4	0.008
108	-	-	-	2.96			0.108
109	1.12	7.13	13.91	0.93	0.85	11.9	0.027
110			2.67	0.02			0.015

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111	0.65	8.49	33.56	0.45	1.11	13.1	0.054
115	1.36	7.81	12.95	1.17	2.00	25.6	0.058
117	0.78	8.69	40.50	0.18	0.28	3.3	0.016
118	1.85	10.97	17.18	0.75	3.32	30.3	0.268
121	-	-	-	0.31			0.055
123	-	-	-	1.43			0.017
125	0.73	15.73	25.36	1.11	2.50	15.9	0.119
233	0.85	23.12	31.90	3.33	6.22	26.9	0.584
379	1.74	51.41	37.54	4.30	16.80	32.7	1.154
382	1.71	73.68	48.81	7.27	36.12	49.0	3.113
387	-	-	-	0.65			0.558
388	0.94	26.10	34.62	0.15	0.68	2.6	0.073
390	1.50	127.63	120.60	23.21	44.20	34.6	1.780
391	1.45	120.92	82.87	24.02	73.24	60.6	2.680
400			104.34	8.55			0.160
408	3.30	25.18	57.40	9.46	4.17	16.6	0.015
410	1.78	29.83	40.08	0.63	2.08	6.7	0.223
414	0.73	26.15	61.89	5.31	6.22	23.8	0.021
416	2.94	230.70	111.17	29.63	156.71	67.9	20.52
418	2.42	209.92	78.55	20.65	77.52	36.9	7.347
421	-	-	-	13.08	19.21		0.206
427	2.85	36.72	50.74	4.16	8.44	23.0	0.440
437	-	-	-	4.21	4.43		0.128
438	2.14	9.05	7.46	0.39	1.86	20.6	0.316

From the foregoing, it will be observed

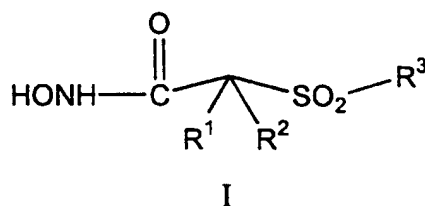
5 that numerous modifications and variations can be effectuated without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation with respect to the specific example presented is

10 intended or should be inferred. The disclosure is intended to cover by the appended claims all such modifications as fall within the scope of the claims.

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WHAT IS CLAIMED:

1. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding in structure to formula (I), below



15

wherein

R^1 and R^2 are both hydrido or R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms in the ring that are oxygen, sulfur or nitrogen;

R^3 is an optionally substituted aryl or optionally substituted heteroaryl radical, and when said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl,

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arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl,
aralkoxyaryl, arylazoaryl, arylhydrazinoaryl,
alkylthioaryl, arylthioalkyl, alkylthioaralkyl,
aralkylthioalkyl, an aralkylthioaryl radical, the
5 sulfoxide or sulfone of any of the thio substituents,
and a fused ring structure comprising two or more 5-
or 6-membered rings selected from the group
consisting of aryl, heteroaryl, cycloalkyl and
heterocycloalkyl, and (b) is itself optionally
10 substituted with one or more substituents
independently selected from the group consisting of a
cyano, perfluoroalkyl, trifluoromethoxy,
trifluoromethylthio, haloalkyl, trifluoromethylalkyl,
aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo,
15 alkyl, alkoxy, nitro, thiol, hydroxycarbonyl,
aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino,
heteroaryloxy, heteroarylthio, heteroaralkyl,
cycloalkyl, heterocyclooxy, heterocyclothio,
heterocycloamino, cycloalkyloxy, cycloalkylthio,
20 heteroaralkoxy, heteroaralkylthio, aralkoxy,
aralkylthio, aralkylamino, heterocyclo, heteroaryl,
arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy,
alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy,
aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy,
25 alkylthio, alkoxyalkylthio, alkoxycarbonyl,
aryloxyalkoxyaryl, arylthioalkylthioaryl,
aryloxyalkylthioaryl, arylthioalkoxyaryl,
hydroxycarbonylalkoxy, hydroxycarbonylalkylthio,
alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,
30 wherein the amino nitrogen is (i) unsubstituted,
or (ii) substituted with one or two substituents
that are independently selected from the group
consisting of an alkyl, aryl, heteroaryl,

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aralkyl, cycloalkyl, aralkoxycarbonyl,
alkoxycarbonyl, arylcarbonyl, aralkanoyl,
heteroarylcarbonyl, heteroaralkanoyl and an
alkanoyl group, or (iii) wherein the amino
5 nitrogen and two substituents attached thereto
form a 5- to 8-membered heterocyclo or
heteroaryl ring containing zero to two
additional heteroatoms that are nitrogen, oxygen
or sulfur and which ring itself is (a)
10 unsubstituted or (b) substituted with one or two
groups independently selected from the group
consisting of an aryl, alkyl, heteroaryl,
aralkyl, heteroaralkyl, hydroxy, alkoxy,
alkanoyl, cycloalkyl, heterocycloalkyl,
15 alkoxycarbonyl, hydroxyalkyl, trifluoromethyl,
benzofused heterocycloalkyl, hydroxyalkoxyalkyl,
aralkoxycarbonyl, hydroxycarbonyl,
aryloxycarbonyl, benzofused heterocycloalkoxy,
benzofused cycloalkylcarbonyl, heterocyclo-
20 alkylcarbonyl, and a cycloalkylcarbonyl group,
carbonylamino
wherein the carbonylamino nitrogen is (i)
unsubstituted, or (ii) is the reacted amine of
an amino acid, or (iii) substituted with one or
25 two radicals selected from the group consisting
of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl,
cycloalkyl, aralkyl, trifluoromethylalkyl,
heterocycloalkyl, benzofused heterocycloalkyl,
benzofused heterocycloalkyl, benzofused
30 cycloalkyl, and an N,N-dialkylsubstituted
alkylamino-alkyl group, or (iv) the carboxamido
nitrogen and two substituents bonded thereto
together form a 5- to 8-membered heterocyclo,

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heteroaryl or benzofused heterocycloalkyl ring
that is itself unsubstituted or substituted with
one or two radicals independently selected from
the group consisting of an alkyl,
5 alkoxycarbonyl, nitro, heterocycloalkyl,
hydroxy, hydroxycarbonyl, aryl, aralkyl,
heteroaralkyl and an amino group,

wherein the amino nitrogen is
(i) unsubstituted, or (ii) substituted with
10 one or two substituents that are
independently selected from the group
consisting of alkyl, aryl, and heteroaryl,
or (iii) wherein the amino nitrogen and two
substituents attached thereto form a 5- to
15 8-membered heterocyclo or heteroaryl ring,
and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i)
unsubstituted, or (ii) substituted with one or two
substituents independently selected from the group
20 consisting of an alkyl, aryl, aralkyl, cycloalkyl,
aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl
group, or (iii) wherein the aminoalkyl nitrogen and
two substituents attached thereto form a 5- to 8-
membered heterocyclo or heteroaryl ring.

25

2. The process according to claim 1
wherein R¹ and R² together with the atoms to which
they are bonded form a 5- to 8-membered ring
containing one, two or three heteroatoms in the ring
30 that are oxygen, sulfur or nitrogen;

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3. The process according to claim 2
wherein R^3 is a single-ringed aryl or heteroaryl
group that is 5- or 6-membered, and is itself
substituted at its own 4-position when a 6-membered
5 ring or at its own 3- or 4-position when a 5-membered
ring with a substituent selected from the group
consisting of one other single-ringed aryl or
heteroaryl group, a C_3 - C_{14} alkyl group, a N-piperidyl
group, a N-piperazinyl group, a phenoxy group, a
10 thiophenoxy group, a 4-thiopyridyl group, a phenylazo
group and a benzamido group.

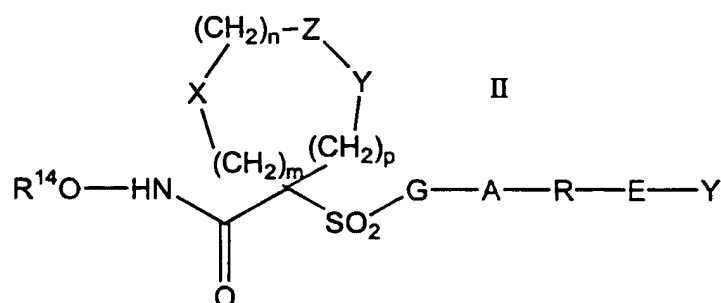
4. The process according to claim 3
wherein R^3 contains two or more 5- or 6-membered
15 rings.

5. The process according to claim 3
wherein R^3 , when rotated about an axis drawn through
the SO_2 -bonded 1-position and the substituent-bonded
20 4-position of a 6-membered ring or the SO_2 -bonded 1-
position and substituent-bonded 3- or 4-position of a
5-membered ring, defines a three-dimensional volume
whose widest dimension has the width in a direction
transverse to that axis to rotation of about one
25 furanyl ring to about two phenyl rings.

6. The process according to claim 3
wherein R^3 has a length that is greater than that of
a pentyl group and a length that is less than that of
30 an icosyl group.

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7. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or
 5 a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory
 10 activity against MMP-1, said compound corresponding in structure to formula II, below



15 wherein

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of a C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl,
 20 C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, aryloxy, ar- C_1 - C_6 -alkoxy, ar- C_1 - C_6 -alkyl, heteroaryl and amino C_1 - C_6 -alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group
 25 consisting of an C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl,

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C₃-C₈-cycloalkyl-C₁-C₆-alkyl, ar-C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl, and C₁-C₆-alkanoyl radical, or (iii) wherein the amino C₁-C₆-alkyl nitrogen and two substituents attached thereto
5 form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

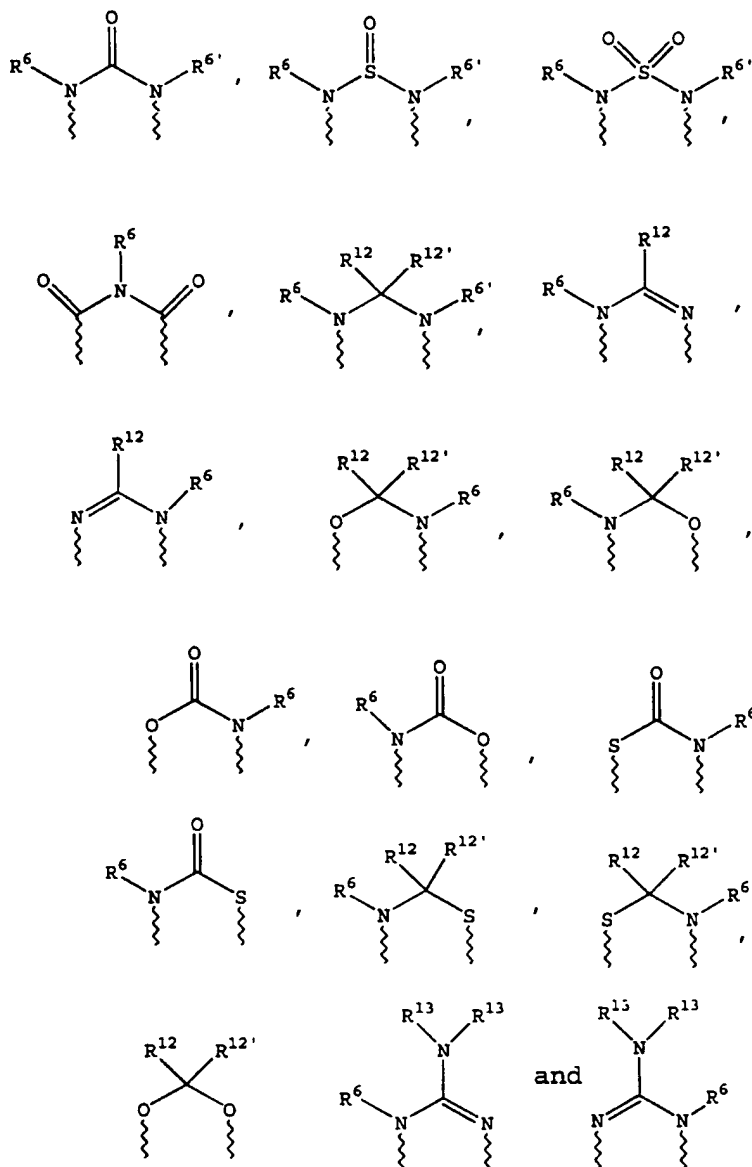
10 the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR⁶, O, S, S(O), S(O)₂ and NS(O)₂R⁷, and the remaining two of X, Y and Z are CR⁸R⁹, and CR¹⁰R¹¹, or

15 (b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of NR⁶C(O), NR⁶S(O), NR⁶S(O)₂, NR⁶S, NR⁶O, SS, NR⁶NR⁶ and OC(O), with the remaining one of X, Y and Z being CR⁸R⁹, or

20 (c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of

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5 wherein wavy lines are bonds to the atoms
of the depicted ring;

R^6 and $R^{6'}$ are independently selected from
the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -
aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -
10 alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 -
 C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -

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- perfluoroalkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is
- (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein
- the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a

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C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group
5 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group
10 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;
15

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl,
20 hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or
25

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sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is

5 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a

10 carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or

15 sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl,

20 cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl,

25 aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-

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alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein
5 the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting
10 of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

G-A-R-E-Y is a substituent that has a length greater than that of a pentyl group has a
15 length that is less than that of an icosyl group wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- 20 (1) -O-;
(2) -S-;
(3) -NR¹⁷-;
(4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
(5) -CO-O- or -O-CO-;
25 (6) -O-CO-O-;
(7) -HC=CH-;
(8) -NH-CO-NH-;
(9) -C≡C-;
(10) -NH-CO-O- or -O-CO-NH-;

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(11) -N=N-;

(12) -NH-NH-; and

(13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, whereinR¹⁸ is hydrogen C₁-C₄-alkyl, or

5 phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a

10 heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio,

20 trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl

25 group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is a heterocycloalkyl, or a cycloalkyl

30 group;

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(2) -CONH- or -HNCO-; and

(3) -CO-;

(4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;

(5) -SO₂-;

5 (6) -NH-SO₂- or -SO₂-NH-; or

(7) E is absent and R is bonded directly
to Y; and

Y is absent or is selected from the group
consisting of a hydrido, alkyl, alkoxy, haloalkyl,
10 aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy,
aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl,
perfluoroalkoxy, perfluoroalkylthio,
trifluoromethylalkyl, alkenyl, heterocycloalkyl,
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a
15 aminoalkyl group, wherein the aryl or heteroaryl or
heterocycloalkyl group is (i) unsubstituted or (ii)
substituted with one or two radicals independently
selected from the group consisting of an alkanoyl,
halo, nitro, aralkyl, aryl, alkoxy, and an amino
20 group wherein the amino nitrogen is (i) unsubstituted
or (ii) substituted with one or two groups
independently selected from hydrido, alkyl, and an
aralkyl group.

25 8. The process according to claim 7
wherein said -G-A-R-E-Y substituent contains two to
four carbocyclic or heterocyclic rings.

9. The process according to claim 8
30 wherein each of the two to four rings is 6-membered.

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10. The process according to claim 7 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

5

11. The process according to claim 7 wherein A is -O- or -S-.

12. The process according to claim 7
10 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

13. The process according to claim 7 wherein E is absent.

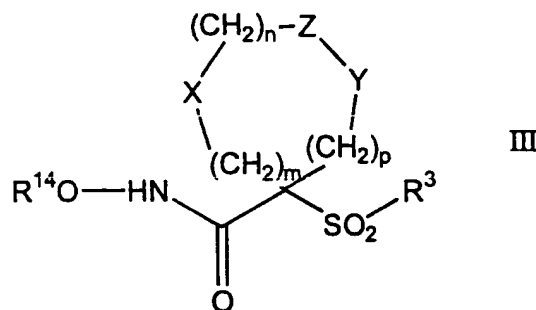
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14. The process according to claim 7 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

20

15. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or
25 a pharmaceutically acceptable salt thereof in an effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory
30 activity against MMP-1, said compound corresponding in structure to formula III, below

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wherein

R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chloro-phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxyphenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)phenoxy, 4-(trifluoromethylthio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinylxyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, and a 4-benzyloxyphenoxy group;

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R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of a C_1-C_6 -alkyl, aryl, C_1-C_6 -alkoxy, heteroaryl- C_1-C_6 -alkyl, C_3-C_8 -cycloalkyl- C_1-C_6 -alkyl, aryloxy, ar- C_1-C_6 -alkoxy, ar- C_1-C_6 -alkyl, heteroaryl and amino C_1-C_6 -alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1-C_6 -alkyl, aryl, ar- C_1-C_6 -alkyl, C_3-C_8 -cycloalkyl- C_1-C_6 -alkyl, ar- C_1-C_6 -alkoxycarbonyl, C_1-C_6 -alkoxycarbonyl, and C_1-C_6 -alkanoyl radical, or (iii) wherein the amino C_1-C_6 -alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

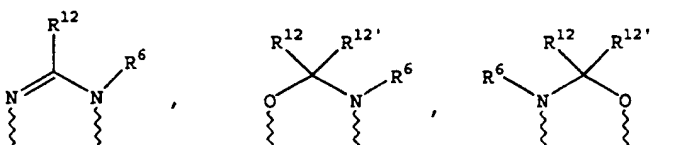
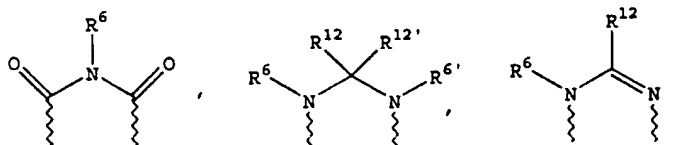
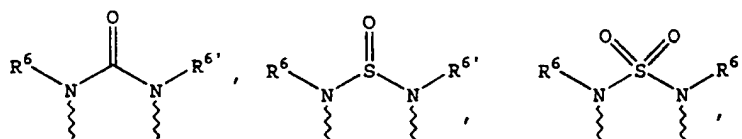
the sum of $m + n + p = 1, 2, 3$ or 4;

(a) one of X, Y and Z is selected from the group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$ and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9 , and $CR^{10}R^{11}$, or

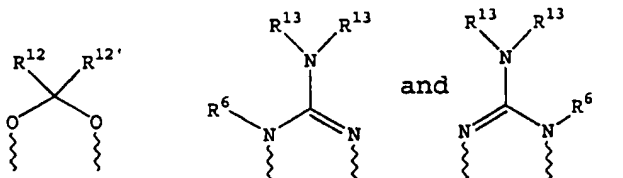
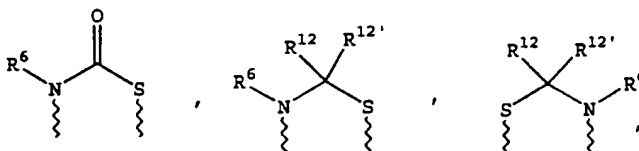
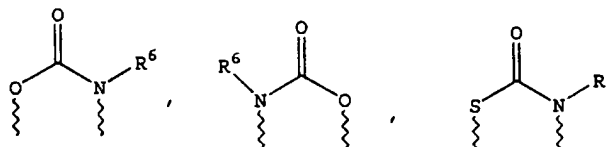
(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S , NR^6O , SS, NR^6NR^6 and $OC(O)$, with the remaining one of X, Y and Z being CR^8R^9 , or

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(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



5



wherein wavy lines are bonds to the atoms
10 of the depicted ring;

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R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 -
 5 C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_8 -heterocycloalkyl, C_3 - C_8 -heterocycloalkylcarbonyl, C_6 -aryl, C_5 - C_6 -heterocyclo, C_5 - C_6 -heteroaryl, C_3 - C_8 -cycloalkyl- C_1 -
 10 C_6 -alkyl, C_6 -aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, heteroarylthio- C_1 - C_6 -alkyl, C_6 -arylsulfonyl, C_1 - C_6 -alkylsulfonyl, C_5 - C_6 -heteroarylsulfonyl, carboxy- C_1 - C_6 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_6 -alkyl,
 15 aminocarbonyl, C_1 - C_6 -alkyliminocarbonyl, C_6 -aryliminocarbonyl, C_5 - C_6 -heterocycloiminocarbonyl, C_6 -arylthio- C_1 - C_6 -alkyl, C_1 - C_6 -alkylthio- C_1 - C_6 -alkyl, C_6 -arylthio- C_3 - C_6 -alkenyl, C_1 - C_4 -alkylthio- C_3 - C_6 -alkenyl, C_5 - C_6 -heteroaryl- C_1 - C_6 -alkyl, halo- C_1 - C_6 -
 20 alkanoyl, hydroxy- C_1 - C_6 -alkanoyl, thiol- C_1 - C_6 -alkanoyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, C_1 - C_5 -alkoxycarbonyl, aryloxycarbonyl, NR^8R^9 - C_1 - C_5 -alkylcarbonyl, hydroxy- C_1 - C_5 -alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is
 25 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1 - C_6 -alkyl, ar- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl and a C_1 - C_6 -alkanoyl group,

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hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of

5 C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group

10 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group

15 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-

20 carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-

25 C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl,

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hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-

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C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl,
aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl,
heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-
alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-
5 alkyl, the sulfoxide or sulfone of any said thio
substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-
C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-
C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein
the aminoalkyl nitrogen is (i) unsubstituted or (ii)
10 substituted with one or two radicals independently
selected from the group consisting of C₁-C₆-alkyl,
ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl; and
R¹³ is selected from the group consisting
of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-
15 alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl
group.

16. The process according to claim 15
wherein the sum of m + n + p = 1 or 2.

20

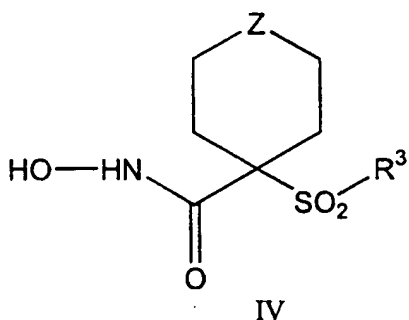
17. The process according to claim 15
wherein Z is O, S or NR⁶.

18. The process according to claim 15
25 wherein R⁶ is selected from the group consisting of
C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₃-C₆-alkenyl, C₃-C₆-
alkynyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl,
aminosulfonyl, heteroaryl-C₁-C₆-alkyl,
aryloxycarbonyl, and C₁-C₆-alkoxycarbonyl.

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19. The process according to claim 15 wherein $m = n = \text{zero}$, $p = 1$, and Y is NR^6 .

5 20. A process for treating a host mammal having a condition associated with pathological matrix metalloprotease (MMP) activity that comprises administering a metalloprotease inhibitor compound or a pharmaceutically acceptable salt thereof in an
10 effective amount to a mammalian host having such a condition, said metalloprotease inhibitor inhibiting the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1, said compound corresponding
15 in structure to formula IV, below



 wherein R^3 is an optionally substituted aryl or optionally substituted heteroaryl radical,
20 and when said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy,
25 aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl,

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aralkoxyaryl, arylazoaryl, arylhydrazinoaryl,
alkylthioaryl, arylthioalkyl, alkylthioaralkyl,
aralkylthioalkyl, an aralkylthioaryl radical, the
sulfoxide or sulfone of any of the thio substituents,
5 and a fused ring structure comprising two or more 5-
or 6-membered rings selected from the group
consisting of aryl, heteroaryl, cycloalkyl and
heterocycloalkyl, and (b) is itself optionally
substituted with one or more substituents
10 independently selected from the group consisting of a
cyano, perfluoroalkyl, trifluoromethoxy,
trifluoromethylthio, haloalkyl, trifluoromethylalkyl,
aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo,
alkyl, alkoxy, nitro, thiol, hydroxycarbonyl,
15 aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino,
heteroaryloxy, heteroarylthio, heteroaralkyl,
cycloalkyl, heterocyclooxy, heterocyclothio,
heterocycloamino, cycloalkyloxy, cycloalkylthio,
heteroaralkoxy, heteroaralkylthio, aralkoxy,
20 aralkylthio, aralkylamino, heterocyclo, heteroaryl,
arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy,
alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy,
aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy,
alkylthio, alkoxyalkylthio, alkoxycarbonyl,
25 aryloxyalkoxyaryl, arylthioalkylthioaryl,
aryloxyalkylthioaryl, arylthioalkoxyaryl,
hydroxycarbonylalkoxy, hydroxycarbonylalkylthio,
alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,
wherein the amino nitrogen is (i) unsubstituted,
30 or (ii) substituted with one or two substituents
that are independently selected from the group
consisting of an alkyl, aryl, heteroaryl,
aralkyl, cycloalkyl, aralkoxycarbonyl,

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alkoxycarbonyl, arylcarbonyl, aralkanoyl, heteroarylcarbonyl, heteroaralkanoyl and an alkanoyl group, or (iii) wherein the amino nitrogen and two substituents attached thereto

5 form a 5- to 8-membered heterocyclo or heteroaryl ring containing zero to two additional heteroatoms that are nitrogen, oxygen or sulfur and which ring itself is (a) unsubstituted or (b) substituted with one or two

10 groups independently selected from the group consisting of an aryl, alkyl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, alkanoyl, cycloalkyl, heterocycloalkyl, alkoxycarbonyl, hydroxyalkyl, trifluoromethyl, benzofused heterocycloalkyl, hydroxyalkoxyalkyl,

15 aralkoxycarbonyl, hydroxycarbonyl, aryloxycarbonyl, benzofused heterocycloalkoxy, benzofused cycloalkylcarbonyl, heterocycloalkylcarbonyl, and a cycloalkylcarbonyl group,

20 carbonylamino wherein the carbonylamino nitrogen is (i) unsubstituted, or (ii) is the reacted amine of an amino acid, or (iii) substituted with one or two radicals selected from the group consisting

25 of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted

30 alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo, heteroaryl or benzofused heterocycloalkyl ring

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that is itself unsubstituted or substituted with one or two radicals independently selected from the group consisting of an alkyl, alkoxy carbonyl, nitro, heterocycloalkyl, hydroxy, hydroxy carbonyl, aryl, aralkyl, heteroaralkyl and an amino group,

wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of alkyl, aryl, and heteroaryl, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents independently selected from the group consisting of an alkyl, aryl, aralkyl, cycloalkyl, aralkoxy carbonyl, alkoxy carbonyl, and an alkanoyl group, or (iii) wherein the aminoalkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring; and

Z is selected group the group consisting of O, S, NR^6 , SO, SO_2 , and NSO_2R^7 ,

wherein R^6 is selected from the group consisting of hydrido, $\text{C}_1\text{-C}_5\text{-alkyl}$, $\text{C}_1\text{-C}_5\text{-alkanoyl}$, benzyl, benzoyl, $\text{C}_3\text{-C}_5\text{-alkynyl}$, $\text{C}_3\text{-C}_5\text{-alkenyl}$, $\text{C}_1\text{-C}_3\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_3\text{-C}_6\text{-cycloalkyl}$, heteroaryl- $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_5\text{-hydroxyalkyl}$, $\text{C}_1\text{-C}_5\text{-carboxyalkyl}$, $\text{C}_1\text{-}$

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C₅-alkoxy C₁-C₅-alkylcarbonyl, and NR⁸R⁹-C₁-C₅-alkylcarbonyl or NR⁸R⁹-C₁-C₅-alkyl wherein R⁸ and R⁹ are independently hydrido, C₁-C₅-alkyl, C₁-C₅-alkoxycarbonyl or aryl-C₁-C₅-alkoxycarbonyl, or NR⁸R⁹ together form a heterocyclic ring containing 5- to 8-atoms in the ring; and

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group.

21. The process according to claim 20 wherein R³ is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring or at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C₃-C₁₄ alkyl group, a N-piperidyl group, a N-piperazinyl group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo group and a benzamido group.

22. The process according to claim 20 wherein R³ has a length that is greater than that of a pentyl group and a length that is less than that of an icosyl group.

23. The process according to claim 20 wherein Z is O, S or NR⁶.

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24. The process according to claim 23
wherein R^6 is selected from the group consisting of
 C_3-C_6 -cycloalkyl, C_1-C_6 -alkoxy- C_1-C_6 -alkyl, C_1-C_6 -
5 alkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl, amino- C_1-C_6 -
alkyl, aminosulfonyl, heteroaryl- C_1-C_6 -alkyl,
aryloxycarbonyl, and C_1-C_6 -alkoxycarbonyl.

25. The process according to claim 20
10 wherein said R^3 radical is the substituent G-A-R-E-Y,
wherein G is an aryl or heteroaryl group;
A is selected from the group consisting of
(1) -O-;
(2) -S-;
15 (3) - NR^{17} -;
(4) -CO-N(R^{17}) or -N(R^{17})-CO-, wherein R^{17}
is hydrogen, C_1-C_4 -alkyl, or phenyl;
(5) -CO-O- or -O-CO-;
(6) -O-CO-O-;
20 (7) -HC=CH-;
(8) -NH-CO-NH-;
(9) -C \equiv C-;
(10) -NH-CO-O- or -O-CO-NH-;
(11) -N=N-;
25 (12) -NH-NH-; and
(13) -CS-N(R^{18})- or -N(R^{18})-CS-, wherein
 R^{18} is hydrogen C_1-C_4 -alkyl, or
phenyl; or

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(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

- (1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is a heterocycloalkyl, or a cycloalkyl group;
- (2) -CONH- or -HNCO-; and
- (3) -CO-;
- (4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
- (5) -SO₂-;
- (6) -NH-SO₂- or -SO₂-NH-; or

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(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

26. The process according to claim 25 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

27. The process according to claim 26 wherein each of the two to four rings is 6-membered.

28. The process according to claim 25 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

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29. The process according to claim 25 wherein A is -O- or -S-.

30. The process according to claim 25 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

31. The process according to claim 25 wherein E is absent.

10

32. The process according to claim 25 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

15

33. The process according to claim 20 wherein R³ is a radical that is comprised of a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chlorophenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxy-phenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)-phenoxy, 4-(trifluoromethylthio)-thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methylphenoxy, 4-ethoxyphenoxy, 3,4-

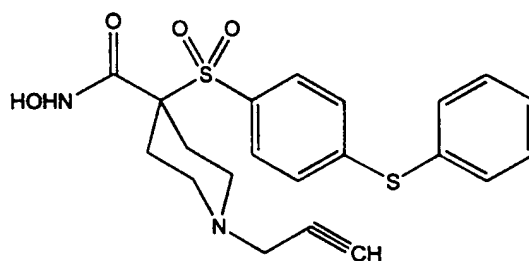
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difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-
 3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy,
 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-
 cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-
 5 bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy,
 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-
 methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-
 2-naphthalenyloxy, 3-hydroxymethylphenoxy, N-
 piperidyl, N-piperazinyl and a 4-benzyloxyphenoxy
 10 group.

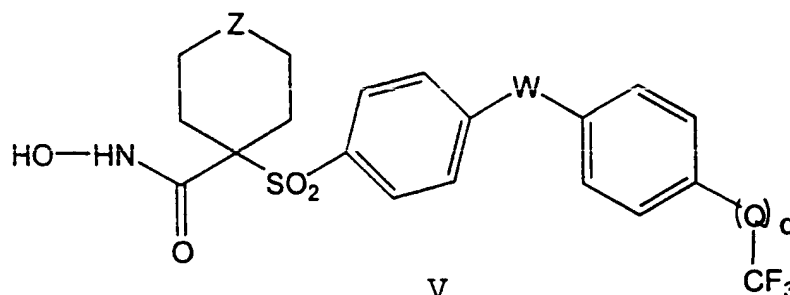
34. The process according to claim 20
 wherein said inhibitor corresponds in structure to
 the formula



15

35. A process for treating a host mammal
 having a condition associated with pathological
 matrix metalloprotease (MMP) activity that comprises
 20 administering a metalloprotease inhibitor compound or
 a pharmaceutically acceptable salt thereof in an
 effective amount to a mammalian host having such a
 condition, said metalloprotease inhibitor inhibiting
 the activity of one or more of MMP-2, MMP-9 and MMP-
 25 13, while exhibiting substantially less inhibitory
 activity against MMP-1, said compound corresponding
 in structure to formula V, below

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wherein

Z is O, S or NR⁶;

5 W and Q are independently oxygen (O), NR⁶
or sulfur (S),

R⁶ is selected from the group consisting of
C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₃-C₆-alkenyl, C₃-C₆-
alkynyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl,
10 aminosulfonyl, heteroaryl-C₁-C₆-alkyl,
aryloxycarbonyl, and C₁-C₆-alkoxycarbonyl; and

q is zero or one such that when q is zero,
Q is absent and the trifluoromethyl group is bonded
directly to the depicted phenyl ring.

15

36. The process according to claim 35
wherein q is zero.

37. The process according to claim 35
20 wherein W is O.

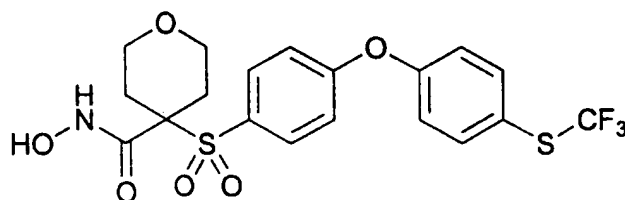
38. The process according to claim 37
wherein q is zero.

25 39. The process according to claim 37
wherein q is one and Q is O.

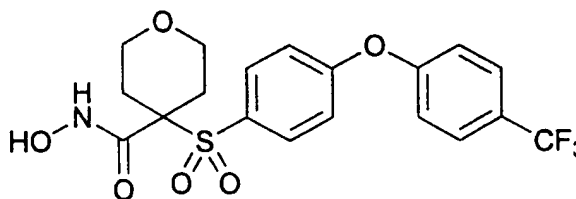
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40. The process according to claim 37
wherein q is one and Q is S.

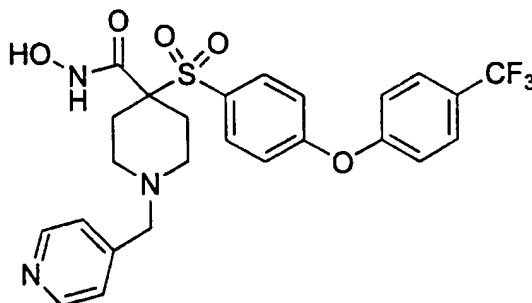
5 41. The process according to claim 35
wherein said inhibitor corresponds in structure to
the formula



42. The process according to claim 35
10 wherein said inhibitor corresponds in structure to
the formula

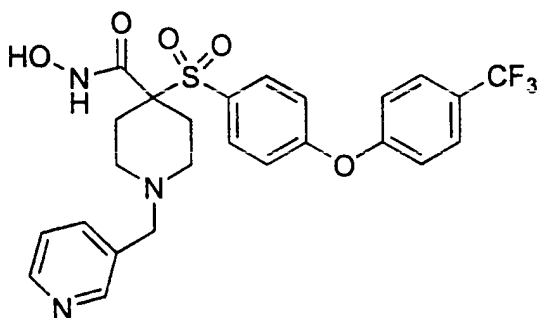


43. The process according to claim 35
wherein said inhibitor corresponds in structure to
15 the formula

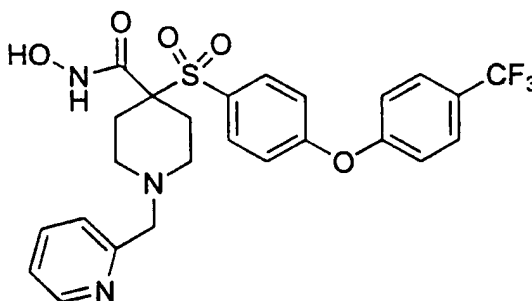


44. The process according to claim 35
wherein said inhibitor corresponds in structure to
the formula

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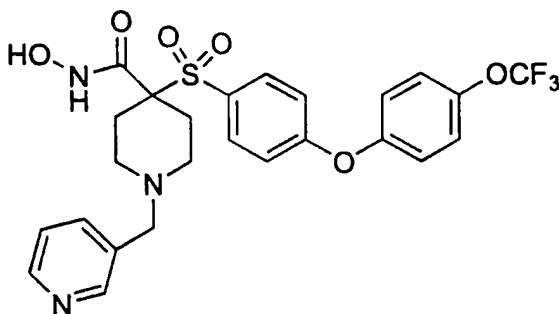


45. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



5

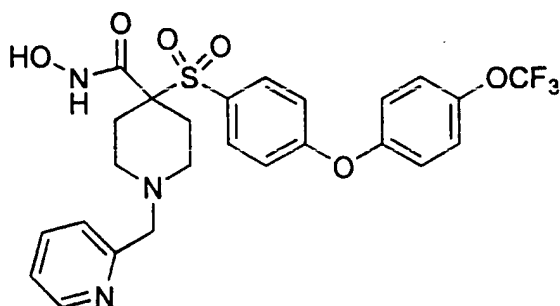
46. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



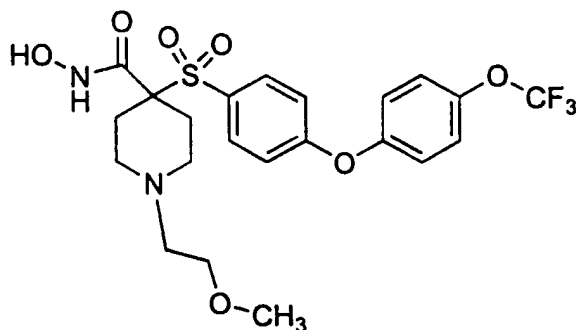
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47. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula

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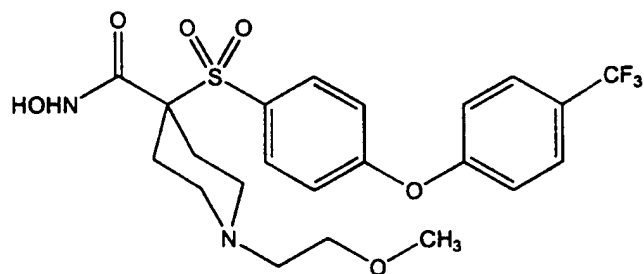


48. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



5

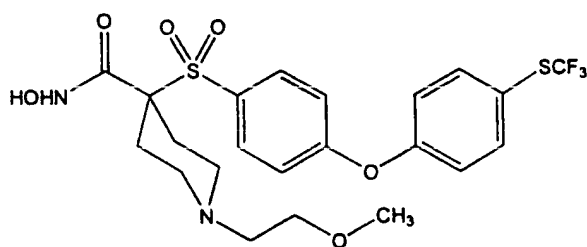
49. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



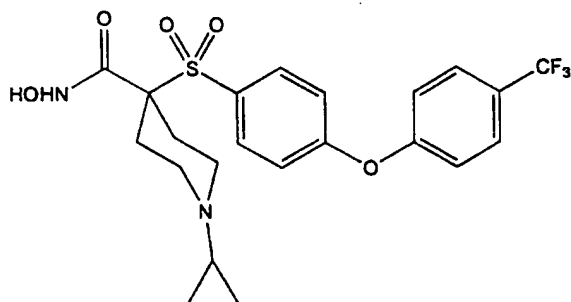
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50. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula

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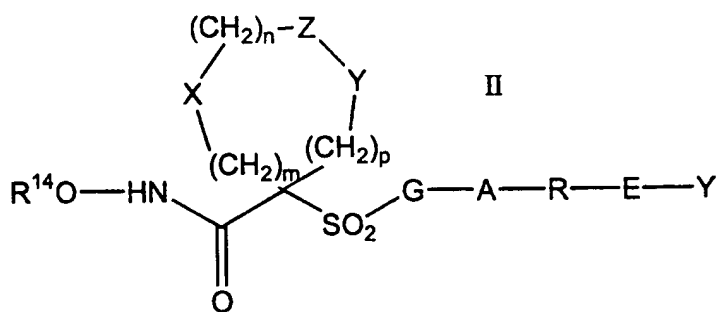


51. The process according to claim 35 wherein said inhibitor corresponds in structure to the formula



5

52. A compound corresponding in structure to formula II, below, or a pharmaceutically acceptable salt thereof:



10

wherein

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of an C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl,

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C₃-C₈-cycloalkyl-C₁-C₆-alkyl, aryloxy, ar-C₁-C₆-alkoxy, ar-C₁-C₆-alkyl, heteroaryl and amino C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, ar-C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl, and C₁-C₆-alkanoyl radical, or (iii) wherein the amino C₁-C₆-alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

15 p is zero, 1 or 2;

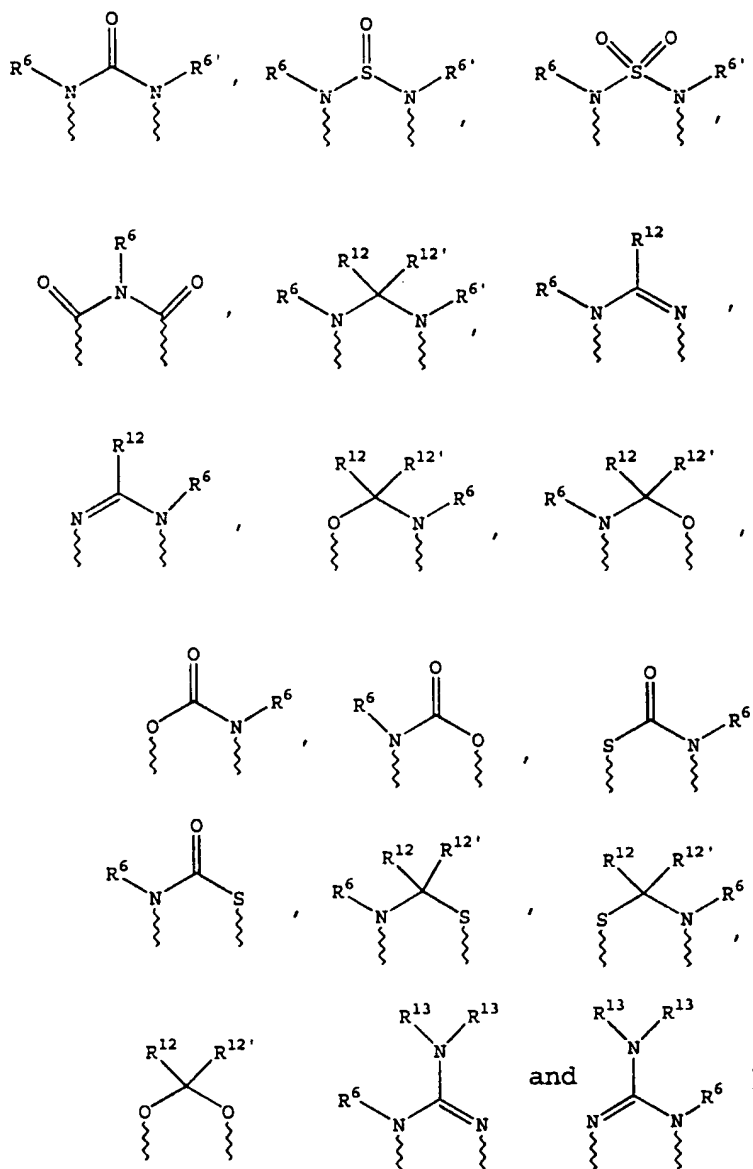
the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR⁶, O, S, S(O), S(O)₂ and NS(O)₂R⁷, and the remaining two of X, Y and Z are
20 CR⁸R⁹, and CR¹⁰R¹¹, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of NR⁶C(O), NR⁶S(O), NR⁶S(O)₂, NR⁶S, NR⁶O, SS, NR⁶NR⁶ and OC(O), with the remaining one of X, Y and Z being
25 CR⁸R⁹, or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of

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5 wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 -
 10 C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -

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- perfluoroalkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is
- 20 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group,
- hydroxyaminocarbonyl, an aminosulfonyl group wherein
- 25 the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a

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C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group
5 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group
10 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-
15 carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-
20 C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl,
25 hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or

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sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is

5 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a

10 carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or

15 sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl,

20 cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl,

25 aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-

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alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein
5 the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting
10 of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

G-A-R-E-Y is a substituent that has a length greater than that of a pentyl group a length
15 that is less than that of an icosyl group, and wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- 20 (1) -O-;
(2) -S-;
(3) -NR¹⁷-;
(4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
(5) -CO-O- or -O-CO-;
25 (6) -O-CO-O-;
(7) -HC=CH-;
(8) -NH-CO-NH-;
(9) -C≡C-;
(10) -NH-CO-O- or -O-CO-NH-;

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(11) -N=N-;

(12) -NH-NH-; and

(13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, whereinR¹⁸ is hydrogen C₁-C₄-alkyl, or

5

phenyl; or

(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a

10 heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl,

20 perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl

25 group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is a heterocycloalkyl, or a cycloalkyl

30

group;

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- (2) -CONH- or -HNCO-; and
(3) -CO-;
(4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
(5) -SO₂-;
5 (6) -NH-SO₂- or -SO₂-NH-; or
(7) E is absent and R is bonded directly
to Y; and

Y is absent or is selected from the group
consisting of a hydrido, alkyl, alkoxy, haloalkyl,
10 aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy,
aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl,
perfluoroalkoxy, perfluoroalkylthio,
trifluoromethylalkyl, alkenyl, heterocycloalkyl,
cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a
15 aminoalkyl group, wherein the aryl or heteroaryl or
heterocycloalkyl group is (i) unsubstituted or (ii)
substituted with one or two radicals independently
selected from the group consisting of an alkanoyl,
halo, nitro, aralkyl, aryl, alkoxy, and an amino
20 group wherein the amino nitrogen is (i) unsubstituted
or (ii) substituted with one or two groups
independently selected from hydrido, alkyl, and an
aralkyl group.

25 53. The compound according to claim 52
wherein said -G-A-R-E-Y substituent contains two to
four carbocyclic or heterocyclic rings.

54. The compound according to claim 52
30 wherein each of the two to four rings is 6-membered.

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55. The compound according to claim 52 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

5

56. The compound according to claim 52 wherein A is -O- or -S-.

57. The compound according to claim 52
10 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

58. The compound according to claim 52 wherein E is absent.

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59. The compound according to claim 52 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

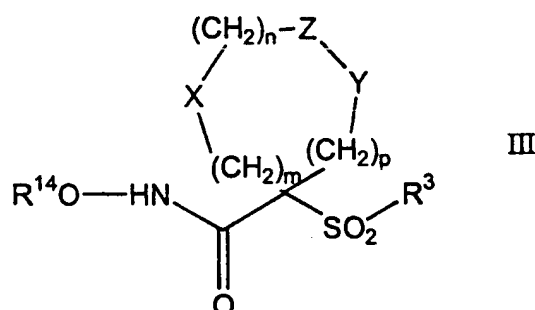
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60. The compound according to claim 52 wherein R^{14} is hydrido.

61. The compound according to claim 52
25 wherein W of the $C(W)R^{15}$ is O and R^{15} is a C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, or aryloxy group.

62. A compound corresponding in structure
30 to formula III, below, or a pharmaceutically acceptable salt thereof

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wherein

- 5 R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the
- 10 group consisting of a thiophenoxy, 4-chloro-phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxyphenoxy, 4-trifluoromethylphenoxy, 4-
- 15 (trifluoromethylthio)phenoxy, 4-(trifluoromethylthio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-
- 20 ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy,
- 25 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-

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tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, and a 4-benzyloxyphenoxy group;

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and

5 R^{15} is selected from the group consisting of a C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, aryloxy, ar- C_1 - C_6 -alkoxy, ar- C_1 - C_6 -alkyl, heteroaryl and amino C_1 - C_6 -alkyl group wherein the aminoalkyl nitrogen is (i)

10 unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, ar- C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkoxycarbonyl, and C_1 - C_6 -

15 alkanoyl radical, or (iii) wherein the amino C_1 - C_6 -alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

20 m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

the sum of $m + n + p = 1, 2, 3$ or 4;

(a) one of X, Y and Z is selected from the group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$

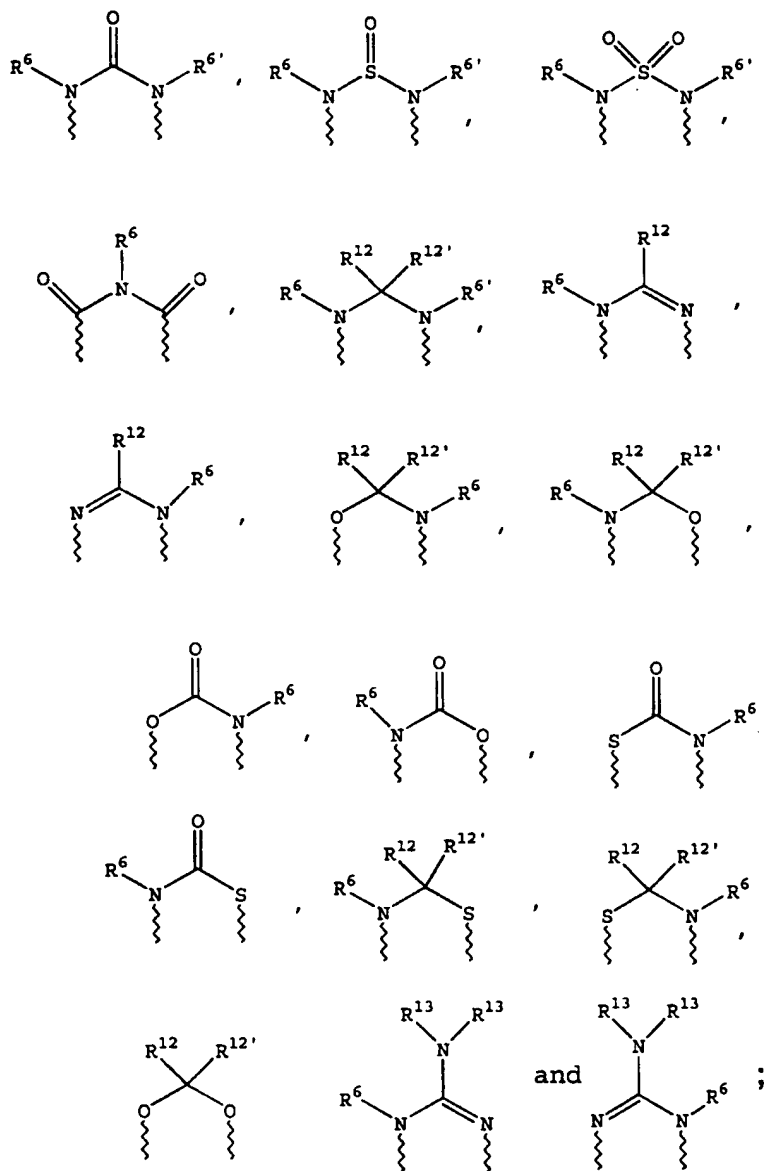
25 and $NS(O)_2R^7$, and the remaining two of X, Y and Z are CR^8R^9 , and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S , NR^6O ,

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SS, NR^6NR^6 and OC(O) , with the remaining one of X, Y and Z being CR^8R^9 , or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group
5 consisting of



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wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -
5 aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -
alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 -
 C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -
perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -
alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_8 -heterocycloalkyl, C_3 -
10 C_8 -heterocycloalkylcarbonyl, C_6 -aryl, C_5 - C_6 -
heterocyclo, C_5 - C_6 -heteroaryl, C_3 - C_8 -cycloalkyl- C_1 -
 C_6 -alkyl, C_6 -aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 -
 C_6 -alkyl, heteroaryl- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl,
heteroarylthio- C_1 - C_6 -alkyl, C_6 -arylsulfonyl, C_1 - C_6 -
15 alkylsulfonyl, C_5 - C_6 -heteroarylsulfonyl, carboxy- C_1 -
 C_6 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_6 -alkyl,
aminocarbonyl, C_1 - C_6 -alkyliminocarbonyl, C_6 -
aryliminocarbonyl, C_5 - C_6 -heterocycloiminocarbonyl,
 C_6 -arylthio- C_1 - C_6 -alkyl, C_1 - C_6 -alkylthio- C_1 - C_6 -alkyl,
20 C_6 -arylthio- C_3 - C_6 -alkenyl, C_1 - C_4 -alkylthio- C_3 - C_6 -
alkenyl, C_5 - C_6 -heteroaryl- C_1 - C_6 -alkyl, halo- C_1 - C_6 -
alkanoyl, hydroxy- C_1 - C_6 -alkanoyl, thiol- C_1 - C_6 -
alkanoyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_1 - C_4 -alkoxy-
 C_1 - C_4 -alkyl, C_1 - C_5 -alkoxycarbonyl, aryloxycarbonyl,
25 NR^8R^9 - C_1 - C_5 -alkylcarbonyl, hydroxy- C_1 - C_5 -alkyl, an
aminocarbonyl wherein the aminocarbonyl nitrogen is
(i) unsubstituted or (ii) substituted with one or two
radicals independently selected from the group

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consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or

5 (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen

10 is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is

15 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of

20 a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido,

25 hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-

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alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-

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- alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl; and
- 15 R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group.
- 20 63. The compound according to claim 62 wherein the sum of m + n + p = 1 or 2.
64. The compound according to claim 62 wherein Z is O, S or NR⁶.
- 25 65. The compound according to claim 62 wherein R⁶ is selected from the group consisting of C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl,

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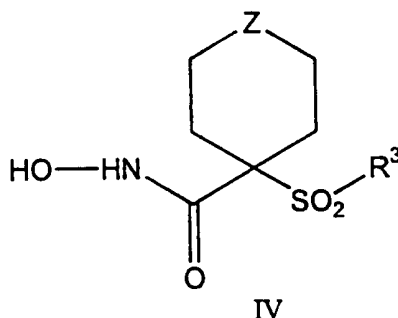
aminosulfonyl, heteroaryl-C₁-C₆-alkyl,
aryloxycarbonyl, and C₁-C₆-alkoxycarbonyl.

66. The compound according to claim 62
wherein m = n = zero, p = 1, and Y is NR⁶.

5 67. The compound according to claim 62
wherein R¹⁴ is hydrido.

68. The compound according to claim 62
wherein W of the C(W)R¹⁵ is O and R¹⁵ is a C₁-C₆-
10 alkyl, aryl, C₁-C₆-alkoxy, heteroaryl-C₁-C₆-alkyl,
C₃-C₈-cycloalkyl-C₁-C₆-alkyl, or aryloxy group.

69. A compound corresponding in structure
to formula IV, below, or a pharmaceutically
15 acceptable salt thereof



wherein R³ is a single-ringed aryl or
heteroaryl group that is 5- or 6-membered, and is
20 itself substituted at its own 4-position when a
6-membered ring or at its own 3- or 4-position when a
5-membered ring with a substituent selected from the
group consisting of one other single-ringed aryl or
heteroaryl group, a C₃-C₁₄ alkyl group, a N-piperidyl
25 group, a N-piperazinyl group, a phenoxy group, a

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thiophenoxy group, a 4-thiopyridyl group, a phenylazo group and a benzamido group; and

Z is selected group the group consisting of O, S, NR⁶, SO, SO₂, and NSO₂R⁷,

5 wherein R⁶ is selected from the group consisting of hydrido, C₁-C₅-alkyl, C₁-C₅-alkanoyl, benzyl, benzoyl, C₃-C₅-alkynyl, C₃-C₅-alkenyl, C₁-C₃-alkoxy-C₁-C₄-alkyl, C₃-C₆-cycloalkyl, heteroaryl-C₁-C₆-alkyl, C₁-C₅-hydroxyalkyl, C₁-C₅-carboxyalkyl, C₁-C₅-alkoxy C₁-C₅-alkylcarbonyl, and NR⁸R⁹-C₁-C₅-alkylcarbonyl or NR⁸R⁹-C₁-C₅-alkyl wherein R⁸ and R⁹ are independently hydrido, C₁-C₅-alkoxy carbonyl or aryl-C₁-C₅-alkoxy carbonyl, or NR⁸R⁹ together form a heterocyclic ring containing 5- to 8- atoms in the ring; and

 R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group.

20

70. The compound according to claim 69 wherein R³ has a length that is greater than that of a pentyl group and a length that is less than that of an icosyl group.

25

71. The compound according to claim 69 wherein Z is O, S or NR⁶.

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72. The compound according to claim 69 wherein R⁶ is selected from the group consisting of C₃-C₆-cycloalkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, amino-C₁-C₆-alkyl, aminosulfonyl, heteroaryl-C₁-C₆-alkyl, aryloxycarbonyl, and C₁-C₆-alkoxycarbonyl.

73. The compound according to claim 69 wherein said R³ radical is the substituent G-A-R-E-Y, wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR¹⁷-;
- (4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -NH-CO-O- or -O-CO-NH-;
- (11) -N=N-;
- (12) -NH-NH-; and
- (13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, wherein R¹⁸ is hydrogen C₁-C₄-alkyl, or phenyl; or

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(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

- (1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is a heterocycloalkyl, or a cycloalkyl group;
- (2) -CONH- or -HNCO-; and
- (3) -CO-;
- (4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
- (5) -SO₂-;
- (6) -NH-SO₂- or -SO₂-NH-; or

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(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

74. The compound according to claim 69 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

75. The compound according to claim 69 wherein each of the two to four rings is 6-membered.

76. The compound according to claim 69 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

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77. The compound according to claim 69 wherein A is -O- or -S-.

78. The compound according to claim 69 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

79. The compound according to claim 69 wherein E is absent.

10

80. The compound according to claim 69 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

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81. The compound according to claim 69 wherein R³ is a radical that is comprised of a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chlorophenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxy-phenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)phenoxy, 4-(trifluoromethylthio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methylphenoxy, 4-ethoxyphenoxy, 3,4-

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difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, N-piperidyl, N-piperazinyl and a 4-benzyloxyphenoxy group.

82. The compound according to claim 69 wherein said R^3 group is a PhR^{23} group, wherein Ph is a phenyl ring that is substituted at its 4-position by an R^{23} group that is a substituent selected from the group consisting of another single-ringed aryl or heteroaryl group, a piperidyl group, a piperazinyl group, a phenoxy group, a thiophenoxy group, a phenylazo group and a benzamido group.

20

83. The compound according to claim 82 wherein said R^{23} group is itself substituted with a moiety that is selected from the group consisting of a halogen, a C_1 - C_4 alkoxy group, a C_1 - C_4 alkyl group, a dimethylamino group, a carboxyl C_1 - C_3 alkylene group, a C_1 - C_4 alkoxy carbonyl C_1 - C_3 alkylene group, a trifluoromethylthio group, a trifluoromethoxy group, a trifluoromethyl group and a carboxamido C_1 - C_3 alkylene group, or is substituted at the meta- and para-positions by a methylenedioxy group.

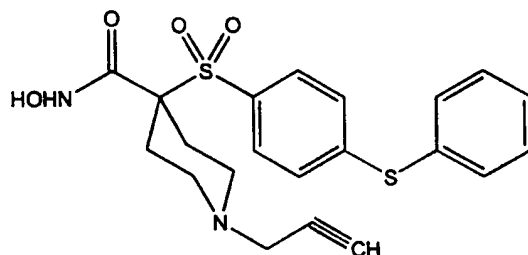
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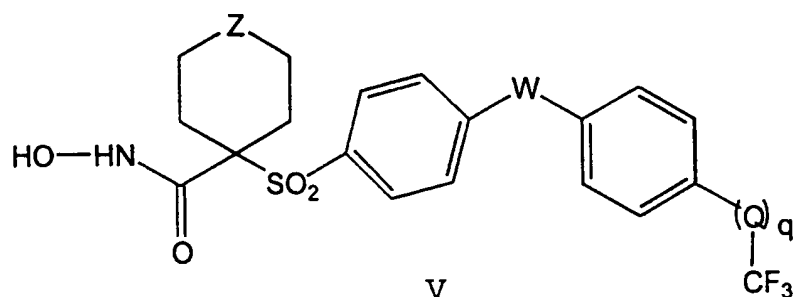
84. The compound according to claim 83 wherein said R^{23} group is substituted at the para-position.

5 85. The compound according to claim 84 wherein said R^{23} group is phenoxy.

86. The compound according to claim 69 wherein said inhibitor corresponds in structure to
10 the formula



87. A compound corresponding in structure to formula V, below, or a pharmaceutically acceptable
15 salt thereof



20 wherein
Z is O, S or NR^6 ;

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W and Q are independently oxygen (O), NR⁶
or sulfur (S),

R⁶ is selected from the group consisting of
C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₃-C₆-alkenyl, C₃-C₆-
5 alkynyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl,
aminosulfonyl, heteroaryl-C₁-C₆-alkyl,
aryloxycarbonyl, and C₁-C₆-alkoxycarbonyl; and

q is zero or one such that when q is zero,
Q is absent and the trifluoromethyl group is bonded
10 directly to the depicted phenyl ring.

88. The compound according to claim 87
wherein q is zero.

15 89. The compound according to claim 87
wherein W is O.

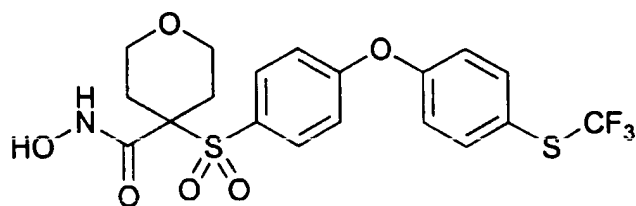
90. The compound according to claim 89
wherein q is zero.
20

91. The compound according to claim 89
wherein q is one and Q is O.

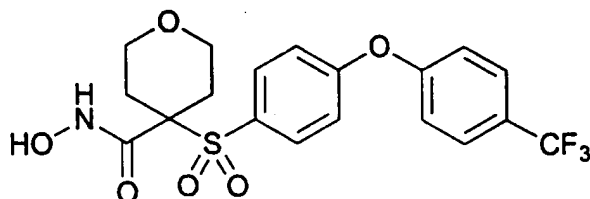
92. The compound according to claim 89
25 wherein q is one and Q is S.

93. The compound according to claim 87
wherein said inhibitor corresponds in structure to
the formula

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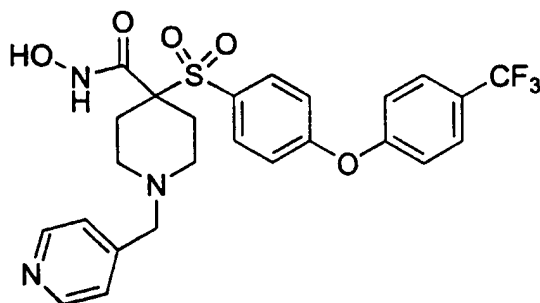


94. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula



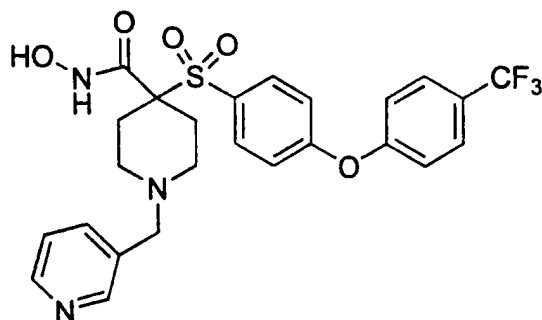
5

95. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula



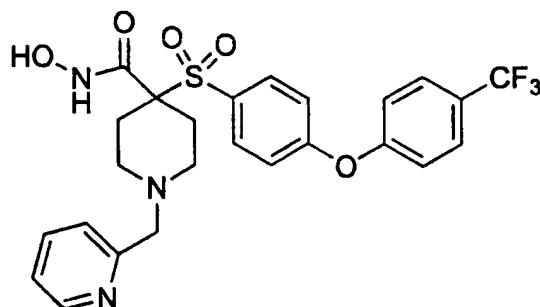
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96. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula

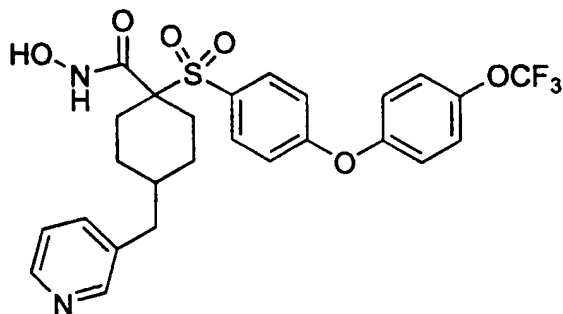


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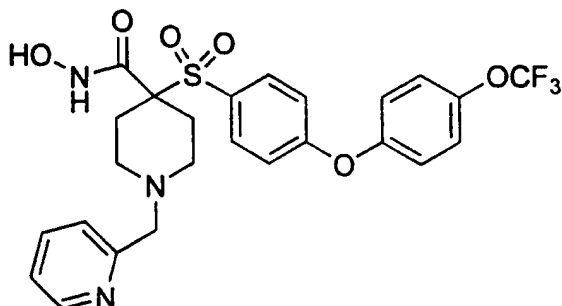
97. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula



5 98. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula

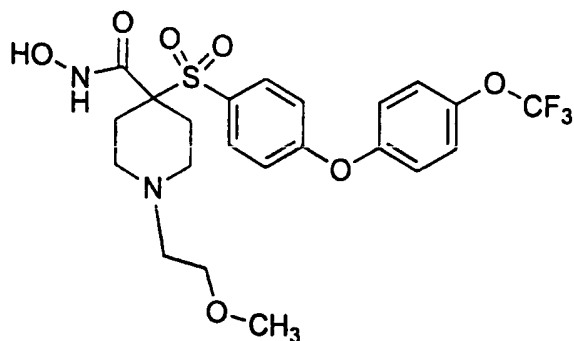


99. The compound according to claim 87
10 wherein said inhibitor corresponds in structure to the formula

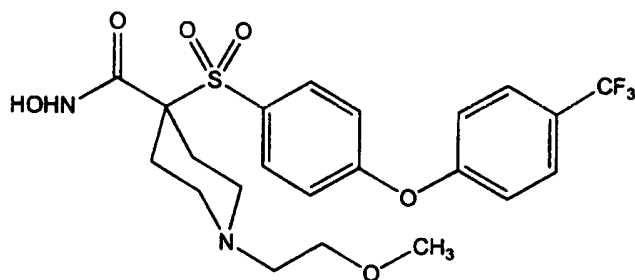


100. The compound according to claim 87
15 wherein said inhibitor corresponds in structure to the formula

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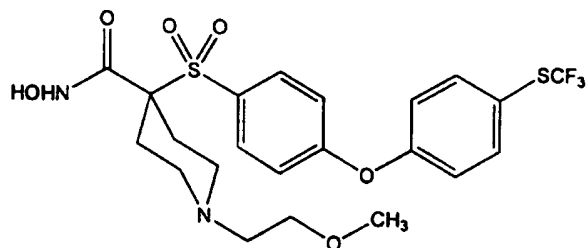


101. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula



5

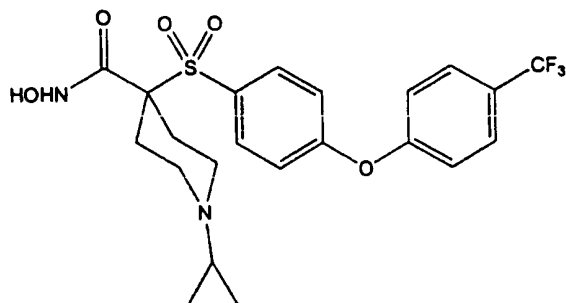
102. The compound according to claim 87 wherein said inhibitor corresponds in structure to the formula



10

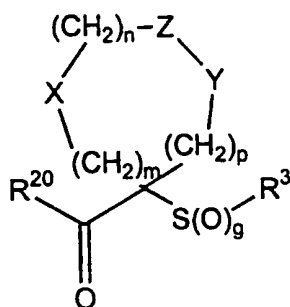
103. The compound according to 87 wherein said inhibitor corresponds in structure to the formula

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104. An intermediate compound
corresponding in structure to formula VI, below

5



VI

wherein

10

g is zero, 1 or 2;

R³ is an optionally substituted aryl or optionally substituted heteroaryl radical, and when said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting
15 of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl,
20 aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl, alkylthioaralkyl,

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aralkylthioalkyl, an aralkylthioaryl radical, the sulfoxide or sulfone of any of the thio substituents, and a fused ring structure comprising two or more 5- or 6-membered rings selected from the group

5 consisting of aryl, heteroaryl, cycloalkyl and heterocycloalkyl, and (b) is itself optionally substituted with one or more substituents independently selected from the group consisting of a cyano, perfluoroalkyl, trifluoromethoxy,

10 trifluoromethylthio, haloalkyl, trifluoromethylalkyl, aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo, alkyl, alkoxy, nitro, thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino, heteroaryloxy, heteroarylthio, heteroaralkyl,

15 cycloalkyl, heterocyclooxy, heterocyclothio, heterocycloamino, cycloalkyloxy, cycloalkylthio, heteroaralkoxy, heteroaralkylthio, aralkoxy, aralkylthio, aralkylamino, heterocyclo, heteroaryl, arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy,

20 alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy, aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy, alkylthio, alkoxyalkylthio, alkoxycarbonyl, aryloxyalkoxyaryl, arylthioalkylthioaryl, aryloxyalkylthioaryl, arylthioalkoxyaryl,

25 hydroxycarbonylalkoxy, hydroxycarbonylalkylthio, alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino, wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group

30 consisting of an alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, arylcarbonyl, aralkanoyl, heteroarylcarbonyl, heteroaralkanoyl and an

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alkanoyl group, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring containing zero to two additional heteroatoms that are nitrogen, oxygen or sulfur and which ring itself is (a) unsubstituted or (b) substituted with one or two groups independently selected from the group consisting of an aryl, alkyl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, alkanoyl, cycloalkyl, heterocycloalkyl, alkoxy carbonyl, hydroxyalkyl, trifluoromethyl, benzofused heterocycloalkyl, hydroxyalkoxyalkyl, aralkoxy carbonyl, hydroxy carbonyl, aryloxy carbonyl, benzofused heterocycloalkoxy, benzofused cycloalkyl carbonyl, heterocycloalkyl carbonyl, and a cycloalkyl carbonyl group, carbonylamino

wherein the carbonylamino nitrogen is (i) unsubstituted, or (ii) is the reacted amine of an amino acid, or (iii) substituted with one or two radicals selected from the group consisting of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo, heteroaryl or benzofused heterocycloalkyl ring that is itself unsubstituted or substituted with one or two radicals independently selected from

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the group consisting of an alkyl,
alkoxycarbonyl, nitro, heterocycloalkyl,
hydroxy, hydroxycarbonyl, aryl, aralkyl,
heteroaralkyl and an amino group,

5 wherein the amino nitrogen is
 (i) unsubstituted, or (ii) substituted with
 one or two substituents that are
 independently selected from the group
 consisting of alkyl, aryl, and heteroaryl,
10 or (iii) wherein the amino nitrogen and two
 substituents attached thereto form a 5- to
 8-membered heterocyclo or heteroaryl ring,
 and an aminoalkyl group

 wherein the aminoalkyl nitrogen is (i)
15 unsubstituted, or (ii) substituted with one or two
 substituents independently selected from the group
 consisting of an alkyl, aryl, aralkyl, cycloalkyl,
 aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl
 group, or (iii) wherein the aminoalkyl nitrogen and
20 two substituents attached thereto form a 5- to 8-
 membered heterocyclo or heteroaryl ring, or is
 an aryl or heteroaryl group that is substituted with
 a nucleophilically displaceable leaving group;

 m is zero, 1 or 2;

25 n is zero, 1 or 2;

 p is zero, 1 or 2;

 the sum of $m + n + p = 1, 2, 3$ or 4;

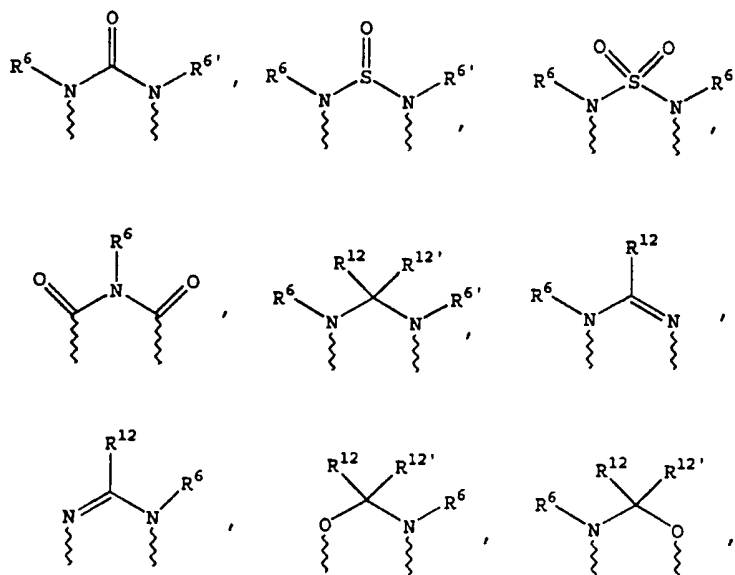
 (a) one of X, Y and Z is selected from the
 group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$ and
30 $NS(O)_2R^7$, and the remaining two of X, Y and Z are
 CR^8R^9 , and $CR^{10}R^{11}$, or

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(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $\text{NR}^6\text{C}(\text{O})$, $\text{NR}^6\text{S}(\text{O})$, $\text{NR}^6\text{S}(\text{O})_2$, NR^6S , NR^6O , SS , NR^6NR^6 and $\text{OC}(\text{O})$, with the remaining one of X, Y and Z being

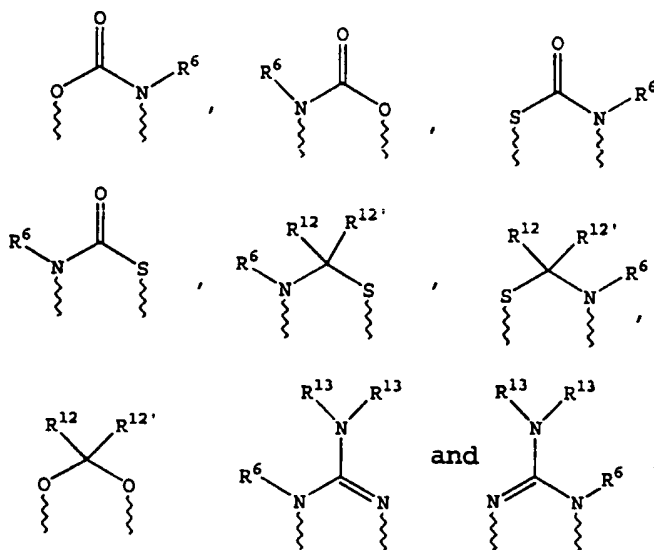
5 CR^8R^9 , or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



10

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wherein wavy lines are bonds to the atoms of the depicted ring;

- 5 R^6 and $\text{R}^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_8 -heterocycloalkyl, C_3 - C_8 -heterocycloalkylcarbonyl, C_6 -aryl, C_5 - C_6 -heterocyclo, C_5 - C_6 -heteroaryl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, C_6 -aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, heteroarylthio- C_1 - C_6 -alkyl, C_6 -arylsulfonyl, C_1 - C_6 -alkylsulfonyl, C_5 - C_6 -heteroarylsulfonyl, carboxy- C_1 - C_6 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_6 -alkyl, aminocarbonyl, C_1 - C_6 -alkyliminocarbonyl, C_6 -
- 10
- 15

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aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl,
C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl,
C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-
alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-
5 alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-
alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-
C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl,
NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an
aminocarbonyl wherein the aminocarbonyl nitrogen is
10 (i) unsubstituted or (ii) substituted with one or two
radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group,
hydroxyaminocarbonyl, an aminosulfonyl group wherein
15 the aminosulfonyl nitrogen is (i) unsubstituted or
(ii) substituted with one or two radicals
independently selected from the group consisting of
C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a
C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl
20 group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen
is (i) unsubstituted or (ii) substituted with one or
two radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group and an amino-
25 C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is
(i) unsubstituted or (ii) substituted with one or two
radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group;

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R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

- 5 R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they

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are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹
5 or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl,
10 cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl,
15 aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-
20 C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl,
25 ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-

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alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

R²⁰ is (a) -O-R²¹, where R²¹ is selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl group and a pharmaceutically acceptable cation, or (b) -NH-O-R²² wherein R²² is a selectively removable protecting group.

105. The intermediate compound according to claim 104 wherein R³ is the substituent G-A-R-E-Y wherein

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- (1) -O-;
- (2) -S-;
- (3) -NR¹⁷-;
- (4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
- (5) -CO-O- or -O-CO-;
- (6) -O-CO-O-;
- (7) -HC=CH-;
- (8) -NH-CO-NH-;
- (9) -C≡C-;
- (10) -NH-CO-O- or -O-CO-NH-;
- (11) -N=N-;
- (12) -NH-NH-; and
- (13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, wherein R¹⁸ is hydrogen C₁-C₄-alkyl, or phenyl; or

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(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, heterocycloalkylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and a heterocycloalkylthioalkyl group wherein the aryl or heteroaryl or cycloalkyl or heterocycloalkyl substituent is (i) unsubstituted or (ii) substituted with one or two radicals selected from the group consisting of a halo, alkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl group, and R is other than alkyl or alkoxyalkyl when A is -O- or -S-;

E is selected from the group consisting of

- (1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is a heterocycloalkyl, or a cycloalkyl group;
- (2) -CONH- or -HNCO-; and
- (3) -CO-;
- (4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
- (5) -SO₂-;
- (6) -NH-SO₂- or -SO₂-NH-; or

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(7) E is absent and R is bonded directly to Y; and

Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

106. The intermediate compound according to claim 104 wherein said -G-A-R-E-Y substituent contains two to four carbocyclic or heterocyclic rings.

107. The intermediate compound according to claim 106 wherein each of the two to four rings is 6-membered.

108. The intermediate compound according to claim 104 wherein said -G-A-R-E-Y substituent has a length that is greater than a hexyl group and a length that is less than that of a stearyl group.

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109. The intermediate compound according to claim 104 wherein A is -O- or -S-.

5 110. The intermediate compound according to claim 104 wherein R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group.

111. The intermediate compound according to claim 104 wherein E is absent.

112. The intermediate compound according to claim 104 wherein Y is selected from the group consisting of hydrido, an alkyl, alkoxy, 15 perfluoroalkoxy and a perfluoroalkylthio group.

113. The intermediate compound according to claim 104 wherein R^{14} is hydrido.

20 114. The intermediate compound according to claim 104 wherein W of the $C(W)R^{15}$ is O and R^{15} is a C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, or aryloxy group.

25 115. The intermediate compound according to claim 103 wherein R^3 is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 30 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from

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the group consisting of a thiophenoxy, 4-chloro-
phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-
benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-
fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-
5 trifluoro-methoxyphenoxy, 4-trifluoromethylphenoxy,
4-(trifluoromethylthio)phenoxy, 4-(trifluoromethyl-
thio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-
isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-
benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy,
10 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-
ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-
methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-
triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-
dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-
15 methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy,
4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-
amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-
tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy,
and a 4-benzyloxyphenoxy group.

20

116. The intermediate compound according
to claim 103 wherein said selectively removable
protecting group is selected from the group
consisting of a 2-tetrahydropyranyl, C₁-C₆-acyl,
25 aroyl, benzyl, p-methoxybenzyloxycarbonyl, .
benzyloxycarbonyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-
alkoxy-CH₂- , C₁-C₆-alkoxy-C₁-C₆-alkoxy-CH₂- and an
o-nitrophenyl group.

30

117. The intermediate compound according
to claim 103 wherein said nucleophilically
displaceable leaving group is selected from the group

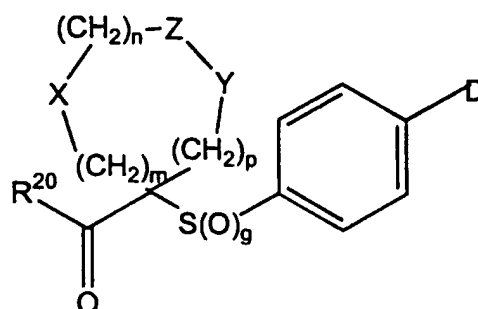
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consisting of a halo, nitro, azido, phenylsulfoxido, aryloxy, C₁-C₆-alkoxy, a C₁-C₆-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are

5 independently aryl, ar- C₁-C₆-alkyl or C₁-C₆-alkyl.

118. The intermediate compound according to claim 103 wherein g is zero.

10 119. An intermediate compound that corresponds in structure to formula VII, below



VII

15 wherein

g is zero, 1 or 2;

D is a nucleophilically displaceable leaving group;

m is zero, 1 or 2;

20 n is zero, 1 or 2;

p is zero, 1 or 2;

the sum of m + n + p = 1, 2, 3 or 4;

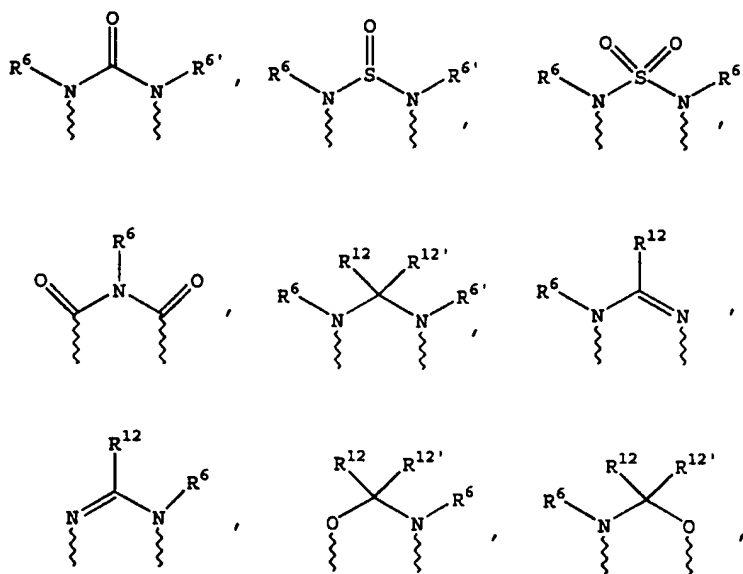
(a) one of X, Y and Z is selected from the group consisting of C(O), NR⁶, O, S, S(O), S(O)₂

-815-

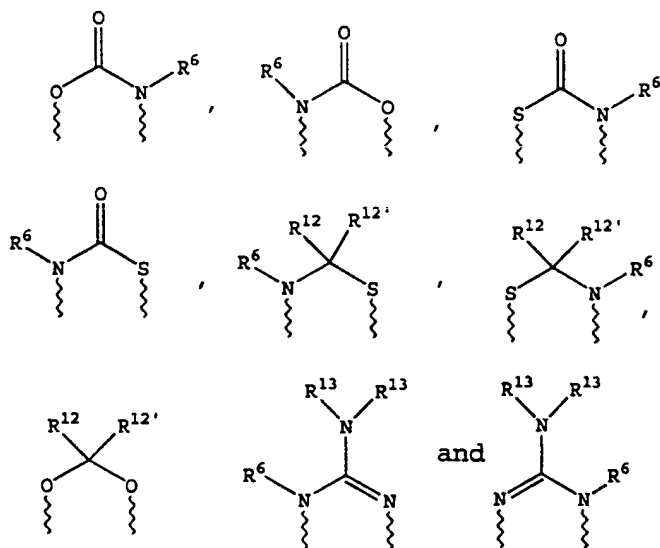
and $\text{NS(O)}_2\text{R}^7$, and the remaining two of X, Y and Z are CR^8R^9 , and $\text{CR}^{10}\text{R}^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of $\text{NR}^6\text{C(O)}$, $\text{NR}^6\text{S(O)}$, $\text{NR}^6\text{S(O)}_2$, NR^6S , NR^6O , SS , NR^6NR^6 and OC(O) , with the remaining one of X, Y and Z being CR^8R^9 , or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of



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wherein wavy lines are bonds to the atoms of the depicted ring;

- 5 R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_8 -heterocycloalkyl, C_3 - C_8 -heterocycloalkylcarbonyl, C_6 -aryl, C_5 - C_6 -heterocyclo, C_5 - C_6 -heteroaryl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, C_6 -aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, heteroarylthio- C_1 - C_6 -alkyl, C_6 -arylsulfonyl, C_1 - C_6 -alkylsulfonyl, C_5 - C_6 -heteroarylsulfonyl, carboxy- C_1 - C_6 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_6 -alkyl, aminocarbonyl, C_1 - C_6 -alkyliminocarbonyl, C_6 -

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aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is

10 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein

15 the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl

20 group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-

25 C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

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R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

- 5 R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they

-819-

are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-

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alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

R²⁰ is (a) -O-R²¹, where R²¹ is selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl group and a pharmaceutically acceptable cation, or (b) -NH-O-R²² wherein R²² is a selectively removable protecting group.

120. The intermediate compound according to 119 wherein said selectively removable protecting group is selected from the group consisting of a 2-tetrahydropyranyl, C₁-C₆-acyl, aroyl, benzyl, p-methoxybenzyloxycarbonyl, benzyloxycarbonyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxy-CH₂- , C₁-C₆-alkoxy-C₁-C₆-alkoxy-CH₂- and an o-nitrophenyl group.

121. The intermediate compound according to claim 119 wherein said nucleophilically displaceable leaving group, D, is selected from the group consisting of a halo, nitro, azido, phenylsulfoxido, aryloxy, C₁-C₆-alkoxy, a C₁-C₆-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar-C₁-C₆-alkyl or C₁-C₆-alkyl.

122. The intermediate compound according to claim 119 wherein said halo group is fluoro.

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123. The intermediate compound according to claim 119 wherein g is zero.

124. A pharmaceutical composition that
5 comprises a compound according to claim 52 dissolved or dispersed in a pharmaceutically acceptable carrier.

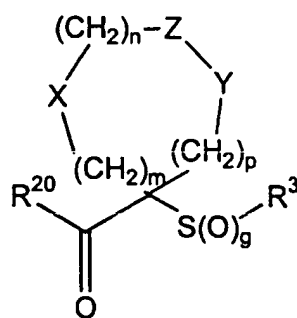
125. A pharmaceutical composition that
10 comprises a compound according to claim 62 dissolved or dispersed in a pharmaceutically acceptable carrier.

126. A pharmaceutical composition that
15 comprises a compound according to claim 69 dissolved or dispersed in a pharmaceutically acceptable carrier.

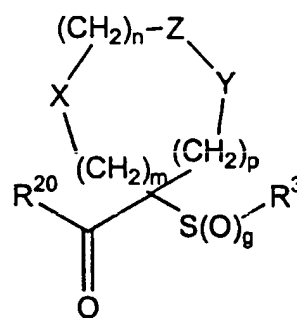
127. A pharmaceutical composition that
20 comprises a compound according to claim 87 dissolved or dispersed in a pharmaceutically acceptable carrier.

128. A process for forming a
25 metalloprotease inhibitor compound product or intermediate compound product therefore that comprises the step of coupling an intermediate compound with another moiety, wherein said intermediate compound corresponds in structure to
30 formula VIB, below, and said product corresponds in structure to formula VIA, below:

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VIA



VIB

wherein

g is zero, 1 or 2;

5 $R^{3'}$ is an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety ;

R^3 is an optionally substituted aryl or optionally substituted heteroaryl radical, and when
 10 said aryl or heteroaryl radical is substituted, the substituent is (a) selected from the group consisting of an optionally substituted cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy,
 15 aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl, aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl, alkylthioaralkyl, aralkylthioalkyl, an aralkylthioaryl radical, the
 20 sulfoxide or sulfone of any of the thio substituents, and a fused ring structure comprising two or more 5- or 6-membered rings selected from the group consisting of aryl, heteroaryl, cycloalkyl and heterocycloalkyl, and (b) is itself optionally
 25 substituted with one or more substituents independently selected from the group consisting of a

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- cyano, perfluoroalkyl, trifluoromethoxy,
trifluoromethylthio, haloalkyl, trifluoromethylalkyl,
aralkoxycarbonyl, aryloxy carbonyl, hydroxy, halo,
alkyl, alkoxy, nitro, thiol, hydroxycarbonyl,
5 aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino,
heteroaryloxy, heteroarylthio, heteroaralkyl,
cycloalkyl, heterocyclooxy, heterocyclothio,
heterocycloamino, cycloalkyloxy, cycloalkylthio,
heteroaralkoxy, heteroaralkylthio, aralkoxy,
10 aralkylthio, aralkylamino, heterocyclo, heteroaryl,
arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy,
alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy,
aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy,
alkylthio, alkoxyalkylthio, alkoxycarbonyl,
15 aryloxyalkoxyaryl, arylthioalkylthioaryl,
aryloxyalkylthioaryl, arylthioalkoxyaryl,
hydroxycarbonylalkoxy, hydroxycarbonylalkylthio,
alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,
wherein the amino nitrogen is (i) unsubstituted,
20 or (ii) substituted with one or two substituents
that are independently selected from the group
consisting of an alkyl, aryl, heteroaryl,
aralkyl, cycloalkyl, aralkoxycarbonyl,
alkoxycarbonyl, arylcarbonyl, aralkanoyl,
25 heteroarylcarbonyl, heteroaralkanoyl and an
alkanoyl group, or (iii) wherein the amino
nitrogen and two substituents attached thereto
form a 5- to 8-membered heterocyclo or
heteroaryl ring containing zero to two
30 additional heteroatoms that are nitrogen, oxygen
or sulfur and which ring itself is (a)
unsubstituted or (b) substituted with one or two
groups independently selected from the group

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- consisting of an aryl, alkyl, heteroaryl,
aralkyl, heteroaralkyl, hydroxy, alkoxy,
alkanoyl, cycloalkyl, heterocycloalkyl,
alkoxycarbonyl, hydroxyalkyl, trifluoromethyl,
5 benzofused heterocycloalkyl, hydroxyalkoxyalkyl,
aralkoxycarbonyl, hydroxycarbonyl,
aryloxycarbonyl, benzofused heterocycloalkoxy,
benzofused cycloalkylcarbonyl, heterocyclo-
alkylcarbonyl, and a cycloalkylcarbonyl group,
10 carbonylamino
wherein the carbonylamino nitrogen is (i)
unsubstituted, or (ii) is the reacted amine of
an amino acid, or (iii) substituted with one or
two radicals selected from the group consisting
15 of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl,
cycloalkyl, aralkyl, trifluoromethylalkyl,
heterocycloalkyl, benzofused heterocycloalkyl,
benzofused heterocycloalkyl, benzofused
cycloalkyl, and an N,N-dialkylsubstituted
20 alkylamino-alkyl group, or (iv) the carboxamido
nitrogen and two substituents bonded thereto
together form a 5- to 8-membered heterocyclo,
heteroaryl or benzofused heterocycloalkyl ring
that is itself unsubstituted or substituted with
25 one or two radicals independently selected from
the group consisting of an alkyl,
alkoxycarbonyl, nitro, heterocycloalkyl,
hydroxy, hydroxycarbonyl, aryl, aralkyl,
heteroaralkyl and an amino group,
30 wherein the amino nitrogen is
(i) unsubstituted, or (ii) substituted with
one or two substituents that are
independently selected from the group

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consisting of alkyl, aryl, and heteroaryl,
or (iii) wherein the amino nitrogen and two
substituents attached thereto form a 5- to
8-membered heterocyclo or heteroaryl ring,
5 and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i)
unsubstituted, or (ii) substituted with one or two
substituents independently selected from the group
consisting of an alkyl, aryl, aralkyl, cycloalkyl,
10 aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl
group, or (iii) wherein the aminoalkyl nitrogen and
two substituents attached thereto form a 5- to 8-
membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

15 n is zero, 1 or 2;

p is zero, 1 or 2;

the sum of $m + n + p = 1, 2, 3$ or 4;

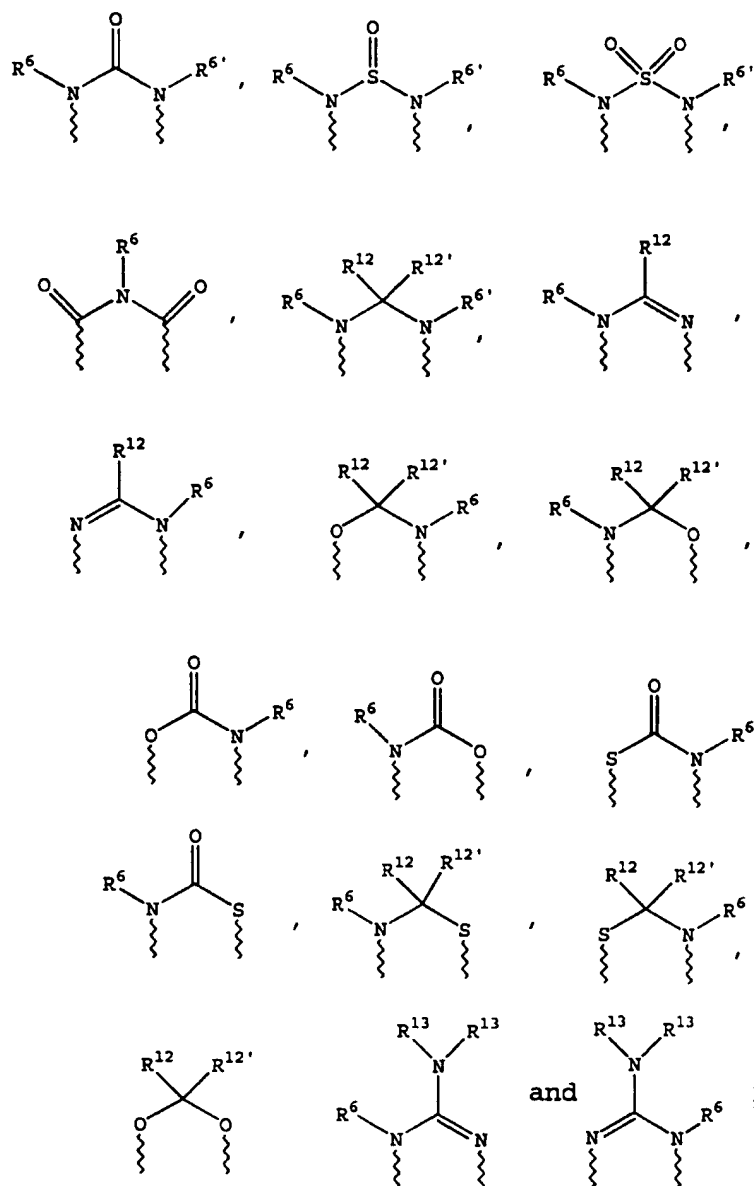
(a) one of X, Y and Z is selected from
the group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$
20 and $NS(O)_2R^7$, and the remaining two of X, Y and Z are
 CR^8R^9 , and $CR^{10}R^{11}$, or

(b) X and Z or Z and Y together
constitute a moiety that is selected from the group
consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S , NR^6O ,
25 SS , NR^6NR^6 and $OC(O)$, with the remaining one of X, Y
and Z being CR^8R^9 , or

(c) n is zero and X, Y and Z together
constitute a moiety selected from the group
consisting of

30

-826-



5 wherein wavy lines are bonds to the atoms of the depicted ring;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -

10

- perfluoroalkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is
- (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein
- the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a

C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or

sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxy-carbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is

5 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a

10 carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or

15 sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-

20 C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-

25 C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-

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alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein
5 the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting
10 of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

R²⁰ is (a) -O-R²¹, where R²¹ is selected from the group consisting of a hydrido, C₁-C₆-alkyl,
15 aryl, ar-C₁-C₆-alkyl group and a pharmaceutically acceptable cation, or (b) -NH-O-R²² wherein R²² is a selectively removable protecting group.

129. The process according to claim 128
20 including the further step of recovering said product.

130. The process according to claim 128 wherein R²⁰ is -NH-O-R²², wherein R²² is a
25 selectively removable protecting group.

131. The process according to claim 130 wherein said selectively removable protecting group is selected from the group consisting of a 2-
30 tetrahydropyranyl, C₁-C₆-acyl, aroyl, benzyl, p-

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methoxybenzyloxycarbonyl, benzyloxycarbonyl, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxy-CH₂- , C₁-C₆-alkoxy-C₁-C₆-alkoxy-CH₂- , an o-nitrophenyl group and a peptide synthesis resin.

5

132. The process according to claim 128 wherein said coupling substituent is a nucleophilically displaceable leaving group

10

133. The process according to claim 122 wherein said nucleophilically displaceable leaving group is selected from the group consisting of a halo, nitro, azido, phenylsulfoxido, aryloxy, C₁-C₆-alkoxy, a C₁-C₆-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar- C₁-C₆-alkyl or C₁-C₆-alkyl.

15

134. The process according to claim 128 wherein g 2.

20

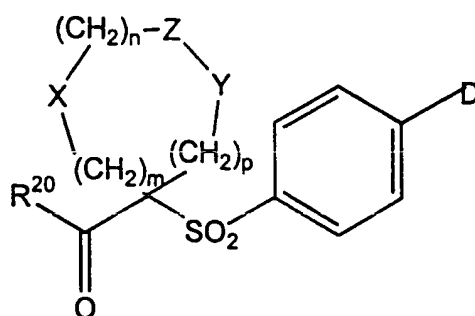
135. The process according to claim 128 wherein said R³ aryl or heteroaryl group is an aryl group.

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136. The process according to claim 128 wherein said intermediate that corresponds in structure to formula VI corresponds in structure to formula VIIA, below,

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VIIA

wherein D is said nucleophilically
displaceable leaving group and is selected from the
group consisting of a halo, nitro, azido,
5 phenylsulfoxido, aryloxy, C₁-C₆-alkoxy, a C₁-C₆-
alkylsulfonate or arylsulfonate group and a
trisubstituted ammonium group in which the three
substituents are independently aryl, ar- C₁-C₆-alkyl
or C₁-C₆-alkyl.

10

137. The process according to claim 128
including the further step of recovering said
product.

15

138. The process according to claim 128
including the further step of selectively removing
said protecting group, R²².

20

139. The process according to claim 138
wherein said protecting group, R²², is removed after
carrying out the further step of recovering said
product.

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140. The process according to claim 139 wherein said protecting group, R^{22} , is a 2-tetrahydropyranyl group.

5 141. The process according to claim 129 wherein R^{21} in said product after recovery is hydrido, and including the further step of reacting said product with hydroxyl amine or a hydroxyl amine whose oxygen is reacted with a selectively removable
10 protecting group selected from the group consisting of a 2-tetrahydropyranyl, C_1-C_6 -acyl, aroyl, benzyl, p-methoxybenzyloxycarbonyl, benzyloxycarbonyl, C_1-C_6 -alkoxycarbonyl, C_1-C_6 -alkoxy- CH_2- , C_1-C_6 -alkoxy- C_1-C_6 -alkoxy- CH_2- , an o-nitrophenyl group and a peptide
15 synthesis resin to form a hydroxamic acid or protected hydroxamate product.

 142. The process according to claim 141 including the further step of recovering the product
20 formed.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23242

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/66 C07D309/08 A61K31/445 A61K31/35 A61K31/16
 C07C317/44 C07D335/02 C07D405/12 C07D409/12 C07D211/94
 C07D405/14 C07D239/04 C07D417/12 C07D407/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 780 386 A (HOFFMANN LA ROCHE ; AGOURON PHARMA (US)) 25 June 1997 cited in the application see the whole document ---	1-142
Y	WO 97 24117 A (RHONE-POULENC RORER PHARMA ; GRONEBERG ROBERT D (US); NEUENSCHWANDE) 10 July 1997 cited in the application see the whole document --- -/-	1-142

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 March 1999

Date of mailing of the international search report

20.04.99

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INTERNATIONAL SEARCH REPORT

Inte. Jonal Application No

PCT/US 98/23242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 9302 Derwent Publications Ltd., London, GB; Class B03, AN 93-012141 XP002095370 & JP 04 338331 A (TAKEDA CHEM IND LTD) , 25 November 1992 see abstract -& JP 04 338331 A (TAKEDA CHEM IND LTD) 25 November 1992 see, in particular, pages 3-4, table 1, the entries no. 7-9, 13, 16, 21, 22, 31, 36, and 41-43</p>	<p>104, 117-119, 121-123</p>
X	<p>EP 0 266 182 A (TAKEDA CHEMICAL INDUSTRIES LTD) 4 May 1988</p> <p>see page 19; claim 1 see page 10; examples 9-11 see page 15; examples 35,38</p>	<p>104, 117-119, 121-123</p>
P,X	<p>WO 98 37877 A (AMERICAN CYANAMID CO) 3 September 1998 see the whole document</p>	<p>1-142</p>
P,X	<p>WO 98 38163 A (AMERICAN CYANAMID CO) 3 September 1998 see the whole document</p>	<p>1-6</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/23242

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 104-120, 122, 123
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 104-120,122,123

The novelty search on the intermediate compounds of formula VI according to the present independent claim 104 - wherein R20 represents the group -O-R21 - revealed a vast amount of novelty-destroying documents. In the case of the said esters (R20 = -O-R21), the International Search Report therefore had to be limited to the intermediates of formula VII of the present claim 119, wherein the group D is defined according to present claim 121 (in the case of the hydroxamic acid derivatives of formula VI (R20 = -NH-O-R22) of the present claim 104, the International Search Report may be considered as being complete).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23242

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